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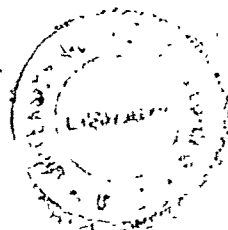
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REVIEW

Prevention of Vesicoureteric Reflux by Endoscopic Injection

P. FREY and R. H. WHITAKER

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In September 1990 a symposium was held in Basle, Switzerland, at which experts were gathered together to try to decide the correct place of injection therapy for vesicoureteric reflux (reflux). Perhaps 2 years before, the same symposium might have been deciding if there was a place at all for such treatment, but that time has now passed and the consensus is clearly that the treatment works and that it is probably here to stay. In 1990 the questions to be answered are how well does it work and how safely? Who should receive the treatment and which substance for injection should be used?

The Need for a Treatment of Reflux

Reflux is a controversial topic, as judged by some 5000 publications on the subject in the last 30 years. Fortunately, there are so many excellent reviews of reflux (Ransley, 1982; Kelalis, 1985; Levitt and Weiss, 1985) that the history and pathophysiology do not need to be expounded here. Suffice it to say that reflux nephropathy accounts for approximately a quarter of all children needing dialysis and transplantation and costs Great Britain alone £20 million per annum for dialysis. Effective early diagnosis and treatment of the anomaly would save vast amounts of money, ill health and misery throughout the world. The search is on to find a diagnostic pathway that can detect reflux before infection occurs and it is clear that only by such means can scarring be avoided (Ransley and Risdon, 1981; Smellie *et al.*, 1985). As soon as reflux is detected some form of treatment is necessary—either conservative or surgical. The arguments for

and against surgery are well known but remain controversial and the overconfidence of proponents of either treatment was modified by the results of the Birmingham study (Birmingham Reflux Study Group, 1983), which suggests that after 5 years of follow-up there is little if any difference between the 2 groups. Although there is probably no consensus as to the exact indications for taking active steps to stop reflux, most would now accept in broad principle that children who continue to suffer repeated urinary infections in the presence of more severe grades of reflux, despite adequate conservative treatment, should be suitable candidates for some form of active prevention.

It should be emphasised that conservative treatment involves not just the prescribing of antibiotics but also regular monitoring of both the urinary bacteriology and the child's bowel and voiding habits, together with the general lowering of anxiety in the family. Reflux is common and perhaps accounts for as many as 25 to 50% of children presenting with urinary infection (Walker *et al.*, 1977; Smellie *et al.*, 1981; Mininberg, 1986; Woodard and Rushton, 1987). In the 1960s and 1970s there was a greater understanding of the aetiology of reflux nephropathy with the introduction of the "big bang theory" (Ransley and Risdon, 1978) and this went a long way to explain why some children showed renal scarring and others, exposed to similar urinary infections, did not and probably will not in the future. It is now well established that spontaneous cessation occurs in approximately 70% of patients with reflux and the effects of long-term prophylactic antibiotics are now proven (Normand and Smellie, 1979; Bellinger and Duckett, 1984). The problem would be so much simpler if reflux was confined to small children, to lesser grades and

always stopped spontaneously, but this is far from the reality. Vesicoureteric reflux is seen in association with duplications of the upper urinary tract and in patients with neuropathic bladder. It can be seen in adults with these pathologies and can also be induced by radiotherapy and by surgeons operating near or in the ureteric orifices, *e.g.* during bladder diverticulectomy or during removal of lower ureteric stones. It may well emerge that it is in some of these situations that the injection technique may have the most to offer.

Conventional Surgery

Of the many operative techniques that have been devised for the prevention of reflux a few have emerged which have stood the test of time, proved reliable, and have become established throughout the world. In the last 10 years the Cohen procedure (Cohen, 1975) has largely overtaken the Leadbetter-Politano method in popularity, but these 2 operative techniques have cornered the market and their excellent results can be used as a baseline against which we can judge the effectiveness of an injection technique. With an open operative method, in most reasonably sized ureters, unassociated with an abnormal bladder and in the hands of a competent surgeon, we are able to offer a 95% success rate with the promise that most of the 5% of failures (persistent reflux and obstruction) can be sorted out by a second operation.

Such an open procedure, however, requires at least a few days in hospital, some mental and physical strain for both the patient and the surgeon and it was thus natural that an alternative treatment should be sought. Could such an alternative and minimally invasive treatment be cost-effective, medically effective, safe and be easier for both the patient and surgeon?

The Development of Endoscopic Injection for Reflux

Matouschek (1981) grasped the nettle and tried injecting under the incompetent ureteric orifice using Teflon paste. He was faced with early failure due to leakage of the material and necrosis of the overlying mucosa. Even in the initially successful cases he realised that late relapse was possible, if not probable. The pioneering work of O'Donnell and Puri (O'Donnell and Puri, 1984; Puri and O'Donnell, 1984) popularised the use of injected Teflon paste to prevent reflux in children. Teflon (polytetrafluoroethylene) is a substance which has

been used for 40 years as an implantation material in living systems. It is used for a variety of techniques 100,000 times annually in the USA. Teflon, a polymer of tetrafluoroethylene, is one of the most inert of known materials and has a low coefficient of friction, high molecular weight, high density, low tensile strength, low modulus of elasticity and low surface tension. There is no proven evidence that it is carcinogenic and although distant migration can occur, no really harmful clinical effects from this have yet been described.

It was successfully validated in animal experiments but workers were sensible to the inevitable initial worries of local sloughing, systemic reactions, induced obstructions, the possibility of snowballing (the injected material engendering an increasing local reaction) or creeping fibrosis. Most of these worries have not been realised and even obstruction, perhaps the most worrying complication, has occurred in only 1 to 2% of procedures.

In addition there were 3 unexpected worries. They found that the glycerol which held the Teflon in suspension was reabsorbed and that the final "mass" was reduced by up to 50%. They also found that pinpoint accuracy was needed to make sure that the most distal part of the ureter was lifted just to the correct extent. No doubt the authors would agree that their third and greatest unexpected worry was the enormous reaction in the profession to such a revolutionary idea—a reaction that polarised those involved with the management of reflux but, ironically, made the symposium in Basle both possible and, indeed, essential. As with all major controversies, the stronger the belief is held the less secure are the scientific foundations for such a belief. The sceptics were confronted with a wealth of factual data from throughout the world and the devotees were able to balance their enthusiasm against long-held experience of older methods.

As performed by O'Donnell and his team, the injection of Teflon can give a success rate of up to 90%, sometimes, however, only after several injections but so far relapse is rare after 1 year. Severe reflux may be converted to a lesser degree in some patients. The injection is performed on a day case or short stay basis and is not much more uncomfortable than a simple cystoscopy. There is no doubt that the experience of many surgeons who have tried the technique has proved it to be both minimally invasive and also associated with low morbidity.

Informed consent must be obtained and this means that the alternative treatments and risks must be explained. O'Donnell believes that this

treatment is a genuine alternative to open surgery and thus it should not be denied to the patient.

Technique of Endoscopic Injection

The patient is positioned on his/her back, the legs abducted but not flexed in the hip. The bladder is filled moderately and the needle is inserted 2 to 4 mm below the orifice at 6 o'clock and is advanced for approximately 5 to 6 mm into the subureteric plane of the most distal ureter. Once the tip of the needle is in the correct position, amounts of Teflon up to 0.5 ml, but usually between 0.2 and 0.3 ml, are injected under direct vision. If the injection is performed correctly a submeatal bulge appears immediately, changing the gaping ureteric orifice into a slit. If the orifice is wide open the injection can be made directly through the back wall of the distal ureter and this can be made easier by inserting a small Fogarty balloon catheter up the ureter. By pulling the ureter into the bladder, the correct plane for injection is exposed. There is a risk of injecting into the detrusor muscle or alongside the ureter (rather than under it) or even into the lumen of the ureter. Furthermore, too much Teflon can very occasionally cause obstruction. However, with experience all of these hazards can be avoided.

Results

In O'Donnell's series (O'Donnell, 1991, personal communication), of 123 patients treated between 1984 and 1988 for grades 2–5 reflux (mostly 3–4) there were 98 girls and 25 boys with a mean age of 5.3 years (range 3 months–14 years). Half of the patients had bilateral reflux and in 16 it was associated with a duplication; 149 of 172 ureters stopped refluxing after a first injection and the remainder required between 2 and 4 injections; 116 of the 123 patients were discharged on the day of the procedure. The patients were then followed up for 2 to 6 years and so far 18 have shown recurrence of reflux. There has been no case of late obstruction. Thus 84% of reflux was "cured" with a single injection, 13% with a second and 3% with a third or fourth injection; in 83% success was achieved with only 0.3 ml of Teflon.

Similar results of 83% success after 1 injection and 94.3% after 2 were reported in 450 children by Sauvage *et al.* (1991). These authors also found a 32.3% recurrence rate for grades 3–4 reflux. They suggested that follow-up by ultrasound may be all that is needed and a further cystogram can be reserved for children who continue to have urinary

infections. Although the size of the lump is easily assessed with ultrasound, it has not been found possible to relate this to the risk of failure. Good results are not seen in ectopic ureterocele and they should be excluded.

Surgical exploration for those in whom the injection fails to control reflux is not significantly difficult, but some stiffness of the bladder wall has been observed. Such open operations have shown that failures are due to periureteric or extravescical injection. As with so many fine techniques, attention to detail is essential.

The injection must be performed in the midline of the ureter and under its orifice. A lump must appear the moment the material is injected. In a duplex system the injection must be under each of the orifices and not just between the two.

Post-injection histology is well documented. Teflon spherules are seen in association with macrophages and granuloma formation. Calcification is not uncommon and may be related to the quantity of material that is injected and certainly appears more frequently when the injection is outside the bladder.

In another series (Schulman, personal communication), 256 ureters were evaluated 4 to 5 years after injection and a 90% success rate was achieved after 2 injections (87% after 1). It was found that if the reflux had resolved after 3 months it seldom recurred (in only 2 patients did it return later). Reflux in duplications was treated less successfully—58% resolved after 1 injection and 74% after 2. In this series transient dilatation was seen in 20%, disappearing after 1 month. There were 2 cases of obstruction, 1 on the first post-operative day and the other at 3 months. Both required a reimplantation of the ureter. At the time of open operation in 2 patients who had undergone previous injection, Teflon was found in either the local lymph glands or the ganglia.

Endoscopic Injection in Perspective

In an attempt to redress the balance of opinion and put the technique in clinical context, Philip Ransley pointed out that many of the ureters which are successfully treated by injection would have stopped spontaneously and that these should be separated from the results. It is well known that after 5 years 90% of ureters with grades 1–3 reflux show spontaneous resolution. He felt that a failure rate of 30% in higher grades of reflux compared unfavourably with an open operation but, more important, he questioned the need to correct the

reflux at all in many of the patients who were being treated by this technique.

He suggested that males found to have reflux as a prenatal diagnosis, and in whom urinary infections are uncommon, rarely need any procedure. Girls aged 2 to 3 years with a primary bladder problem can generate high bladder pressures and are at risk of acquired renal scarring, even with lower degrees of reflux. These girls might well be ideal candidates for reflux prevention with the injection technique to tide them over until the time when spontaneous resolution would have occurred.

Safety and the Search for Alternatives to Teflon

The difficulty arises when the patient or parents ask if Teflon is perfectly safe. The fact that some 3000 patients from Europe and the USA have been treated with it is no guarantee. Rames and Aaronson (1991), in an animal experiment, showed, as did Malizia *et al.* (1984, 1987), that Teflon particles can be recovered from both lungs and brain after injections under the distal ureter, and that such distal dispersion is associated with granuloma formation. This may not be of any clinical importance, and indeed Teflon has been used safely for many years for incontinence and for the injection of the vocal cords with no apparent harm. However, the misgivings of injecting foreign substances into small children in the knowledge that such substances will be present for 60 or more years are difficult to assuage.

With these reservations in mind, others have looked for more natural substances to inject and considerable experience has now been amassed using bovine collagen (Zyplast®). The collagen is obtained from cow skin as a triple helical structure. It is treated with a low concentration of glutaraldehyde to cause cross linkage at the site of the lysine bridges, a property that gives it better resistance to the action of collagenases. Also, the terminal telopeptides are removed from the helical collagen structure. The resultant lattice formation is a sterile, highly purified substance with low antigenicity. Injected into the bladder, the collagen paste is changed by body temperature, intracorporeal ionic concentration and pH into a hardish, gel-like substance. Despite the low antigenic properties there may be patients in certain HLA groups who can form antibodies to such denatured collagen. Injectable collagen has been used in plastic surgery to rid patients of facial lines and it has also been injected into vocal cords and used as an embolisation material in over half a million patients.

The injection technique is the same as the one used for Teflon but the injection itself requires far less pressure because the friction coefficient of collagen is much lower. However, it is necessary to inject rather larger volumes, with a mean amount of 1.1 ml. At present some relatively short-term follow-up results are available for assessment.

Results of Collagen Injection

Frey *et al.* (1991b) reported their experience with 82 ureters. In 2 ureters the primary treatment failed. Of the remaining 80 ureters, 61% were free of reflux after 1 injection and 78% after 2, this after a mean follow-up time of 11.5 months. If improvement to grade I and II reflux, generally not requiring further treatment, was included, the success rate after 1 injection was raised to 78% and increased further to 84% after 2 SCIN (subureteric collagen injection) procedures. The subureteric collagen can be easily demonstrated by ultrasound, and is also detectable at open operation, as long as a year after injection. In a histological study, Frey *et al.* (1991a and b) demonstrated that the bovine collagen implants, operatively removed after failed injection treatment, are massively invaded by human fibroblasts followed by active formation of human collagen type I and III. These findings were in accordance with the results of an experimental study in the mini-pig (Frey *et al.*, 1991a).

Cendron *et al.* (1991) used collagen for patients with reflux in whom there was poor compliance with antibiotic therapy or breakthrough infections. It was also used in children with persistent reflux after puberty or after failure of previous surgical treatment. Patients were excluded if there was a positive reaction to skin testing for allergy, pregnancy or severe grades of reflux. They used antibiotic cover and an average amount of collagen of 0.62 ml per patient; 64% of reflux was stopped after 1 treatment and 74% after 2 or 3. They noted that if the reflux resolved at 1 month it remained resolved at 1 year in 78% of ureters. The side effects of clot retention, transient flank pain, bacteriuria and acute pyelonephritis were seen in a few patients but there was no new or worsening upper tract dilatation or allergic reactions. They concluded that the technique was safe and economical with minimal morbidity but was less successful in high grades of reflux; 59% of patients appeared to be cured at 1 year but a subsequent reimplant in others was no problem. The question of the ultimate fate of the collagen was still uncertain but they had no general concern in this respect.

Mohring (personal communication) treated 53 patients with vesicoureteric reflux by subureteric injection of collagen and reported a success rate of 64% after 1 and 73% after 2 injections. Their follow-up time, however, was only 3 to 12 months.

The reputation of collagen was somewhat marred by a report from Lipsky (personal communication), who treated 79 ureters in 51 patients. He found no allergy on testing these patients pre-operatively but subsequently encountered 1 serious allergic reaction at the time of the injection for reflux and another mild one. However, it was not established if the allergic reaction was provoked by bovine collagen or by lignocaine, which is added to the commercially available collagen preparation. After 1 injection, reflux recurred in 25 ureters at 3 to 6 months. In a further 9 ureters in which reflux had stopped, reflux recurred at a later time. This decreased the primary success rate from 63 to 57%. However, he also reported 5 ureters in which there was late spontaneous cessation of reflux after failure of the injection technique; it is most encouraging that this can occur. He concluded that gaping orifices and double orifices were more difficult to treat, that allergies can occur and that the injection technique does not seem to interfere with spontaneous cessation. In addition, it can offer alternatives to long-term chemotherapy and thus may be a major therapy for the future.

The Future

Alternatives to Teflon and collagen must be sought. The ideal substance would be a naturally occurring material that can be homogenised and reinjected. Early experiments with homogenised fat and with blood are showing some promise. The fat is removed by liposuction and it seems that the cells do survive. However, it is too early to report its clinical use.

Conclusion

There is no doubt that one or more injections under the ureteric orifice can stop reflux in approximately 85 to 90% of ureters using Teflon and 65 to 85% using collagen. What remains unclear is which patients should be offered this treatment. O'Donnell would offer it to all patients whilst others would restrict its use to those with failed reimplants, neuropathic bladder or low grades of reflux with repeated infections. Frey believes that the SCIN (subureteric collagen injection) procedure is indicated to replace daily long-term antibiotic prophylaxis

for low grade reflux, especially in patients with low or absent compliance.

Enthusiasts suggest that the technique will eliminate most open operations but others have considerable reservations about the overall efficacy of the technique and express doubts about the safety of Teflon as an injection material.

What is clear is that the technique does not make subsequent open operation more difficult and it does not prevent spontaneous cessation of reflux. The exact role that it will play in the future remains uncertain but it seems that the technique will continue to be used and its place evaluated.

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Changes in Detrusor Innervation with Relief of Outflow Tract Obstruction

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Summary—In 10 patients with urodynamically proven outflow tract obstruction, detrusor biopsies were taken prior to and following relief of obstruction. The changes in detrusor innervation were compared following the relief of obstruction within the study group and also with an age-matched control group who were urodynamically normal. There was a significant reduction in detrusor innervation in the study group when compared with controls pre-operatively. Within the study group there was a significant increase in detrusor innervation in 8 patients following relief of outflow tract obstruction. Persistence of symptoms after prostatectomy may be explained by failure of detrusor reinnervation.

Changes in detrusor innervation as a result of outflow tract obstruction have been documented both in animals (Speakman *et al.*, 1987; Harrison *et al.*, 1990) and in man (Gosling *et al.*, 1986). A reduction in detrusor innervation in man has been shown morphometrically (Gosling *et al.*, 1986) and demonstrated physiologically (Harrison *et al.*, 1987). The persistence of pre-operative urinary symptoms following prostatectomy (Fitzgerald *et al.*, 1979) may be explained by failure of the detrusor innervation to return to normal levels.

The purpose of this study was to examine changes in detrusor innervation in man following relief of outflow tract obstruction using a polyclonal neuronal marker to identify nerve and a morphometric technique to determine innervation density.

Patients and Methods

All male patients attending for routine surveillance cystourethroscopy for superficial transitional cell carcinoma of the urothelium were reviewed symptomatically. Those patients complaining of urinary outflow tract symptoms were offered diagnostic videocystometry.

On the basis of the urodynamic findings, 10 men (mean age 72.7 years; range 60–85) were found to be obstructed. In 9 cases this was defined as a maximum flow rate <15 ml/s and a detrusor pressure of 90 cm H₂O at maximum flow. In the tenth patient the maximum flow rate was 7.5 ml/s with a detrusor pressure of 80 cm H₂O but with unequivocal evidence of prostatic outflow tract obstruction on radiographic screening.

Within this same group of patients a subgroup of 15 men (mean age 66.8 years; range 54–83), with a stable filling cystometrogram and no urodynamic evidence of outflow tract obstruction, formed the controls.

Excluded from these groups were patients with clinical evidence of neurological disease, including diabetic patients, plus those who had received radical radiotherapy for muscle-invasive disease. All patients had undergone initial tumour resection followed by biopsy and diathermy fulguration when indicated. None of the patients in the control or study group had received intravesical chemotherapy as part of their surveillance programme.

At cystourethroscopy, biopsies were taken from the macroscopically normal urothelium of the posterior or lateral walls at least 2 cm away from the trigone and the periureteric areas, avoiding areas of scarring from previous resections. Biopsies

were taken with the bladder half full using cold cup biopsy forceps. Repeat biopsies, from the same area, were taken at the next routine follow-up appointment (mean 4 months; range 3–12).

Following transurethral prostatectomy, the study patients were asked to attend for repeat videocystometry. This was performed in 2 patients; the 8 remaining patients agreed to undergo repeat flow rates and ultrasonic assessment of the post-micturition volume.

Specimen preparation

The specimen was fixed in 10% buffered formaldehyde (British Drug Houses, Poole) for between 6 and 18 h. Following fixation the specimen was paraffin processed. Five micron sections were cut on to L-lysine coated slides. Sections were stained for nerve using a polyclonal antibody to Protein Gene Product 9.5 (PGP 9.5) (Ultraclone Ltd, Cambridge) at a working dilution of 1:400. This was identified using a streptavidin-biotin immunalkaline phosphatase technique with a fast red marker. The slides were counterstained in haematoxylin and blued in lithium carbonate to facilitate muscle identification (Fig.).

All slides were examined at a magnification of $\times 250$ using a Weibel II eye-piece graticule (Graticules Ltd) which delineated the test area; 15 non-

overlapping fields were examined in each section. Within each field the proportion of smooth muscle was assessed using a point counting technique and expressed as a percentage. Only those nerves directly overlying smooth muscle bundles were counted; nerves lying within the interstitial tissue were excluded as these were not felt to represent intimate smooth muscle innervation. Innervation was expressed as the number of nerves per percentage muscle area.

Percentage smooth muscle area, total number of nerves and innervation indices, as defined above, were calculated for each section.

The differences between paired samples were analysed using Student's *t* test. Probability was derived from Fisher Yates probability tables.

Results

Urodynamic results

Urodynamic data for the control and pre-operative study group are shown in Tables 1a and 2.

Of the 10 study patients, 8 had stable detrusor activity on filling. Post-operative urodynamic results in the 2 patients who agreed to undergo repeat videocystometrograms are shown in Table 1b. The free flow rate and ultrasound assessment of residual volume in those patients declining post-operative videocystometry are shown in Table 3.

At review, all patients had symptomatic improvement. In the 2 patients with matched cystometrograms, the maximum flow rate improved in 1, but with a concomitant rise in detrusor pressure; in the second patient (J.M.) the maximum flow rate was unchanged, but at a lower detrusor pressure. In both cases the voiding efficiency, defined as the percentage of bladder capacity voided, was increased. Post-operatively, the second patient had reversal of his unstable detrusor activity.

In the 8 patients who declined post-operative cystometry the maximum and average flow rates increased from pre-operative means of 9.25 and 5.16 ml/s respectively to means of 16 and 10.5 ml/s post-operatively. Improvement in flow rates was associated with a reduction in voiding time and an increase in voiding efficiency. Six patients had no discernible residual volume. Without confirmatory post-operative urodynamics it was not possible to determine whether there was a concomitant reduction in the detrusor voiding pressure.

Biopsy specimen results

Control and study groups. Comparisons were made between the innervation and smooth muscle content

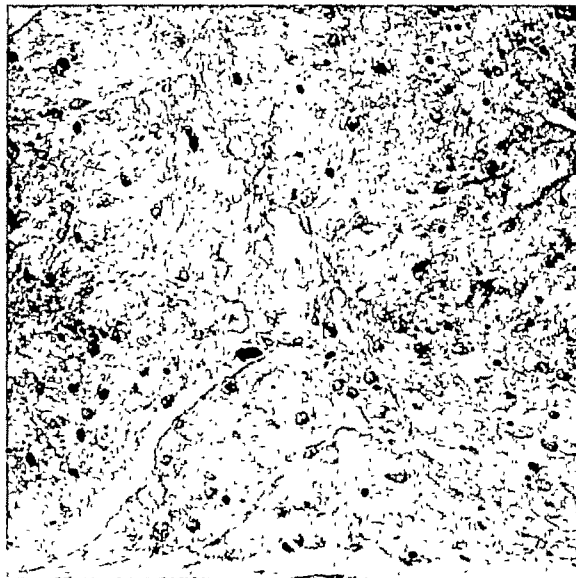


Fig. Detrusor muscle innervation. Typical example of area for nerve counting and application of the Weibel II point counting graticule (PGP 9.5 1:400 dilution, 10% buffered formalin fixation and paraffin processing ($\times 292$))

Table 1a Study Group: Pre-operative Urodynamic Data

<i>Patients</i>	<i>Age (years)</i>	<i>Filled volume (ml)</i>	<i>End detrusor pressure (cm H₂O)</i>	<i>Voided volume (ml)</i>	<i>Voiding time (s)</i>	<i>Max. flow rate (ml/s)</i>	<i>Detrusor pressure at max flow (cm H₂O)</i>	<i>Voiding efficiency (%)</i>
W P	78	500	10	400	60	7.5	80	80
G.W	80	230	50	150	54	15	120	65
K.D.	66	250	20	200	40	10	100	80
J.M	80	360	90	300	36	10	> 100	83
J.R.	73	420	58	300	78	7.5	225	71
D.M.	84	300	15	200	50	7.5	100	67
A.I.	65	440	15	400	65	10	110	90
J.Mc	72	380	20	360	60	10	95	95
D.H.	60	320	20	350	78	10	90	91
J.P.	66	300	30	275	60	5	> 100	92

Table 1b Study Patients: Post-operative Urodynamic Data

W.P.	78	320	15	350	78	10	60	91
J.M.	80	320	40	275	60	10	60	86

Table 2 Control Patients: Urodynamic Data

<i>Patients</i>	<i>Age (years)</i>	<i>Filled volume (ml)</i>	<i>End detrusor pressure (cm H₂O)</i>	<i>Voided volume (ml)</i>	<i>Voiding time (s)</i>	<i>Max. flow rate (ml/s)</i>	<i>Detrusor pressure at max flow (cm H₂O)</i>	<i>Voiding efficiency (%)</i>
C.P.	68	300	20	280	32.4	17.5	70	93
J.M	64	600	10	600	42	25	40	100
C.G	66	900	5	750	30	25	50	83
R.B	83	140	> 100	140	12	15	70	100
J.B.	60	500	5	500	30	25	50	100
W.W.	78	360	60	340	24	15	40	95
W.M.	75	400	10	400	20.4	25	55	100
W.W.	54	240	15	225	22.5	12.5	80	94
P.Mc.	66	480	15	470	24	25	60	100
H.M.	58	450	10	440	30	22.5	40	98
J.Mc.	72	600	20	600	48	20	50	100
W.O	52	300	40	300	24	25	100	100
D.K.	76	330	10	320	30	15	80	97
J.W	72	300	25	450	24	25	30	100
J.B.	53	300	10	290	18	17.5	60	98

Table 3 Study Group: Post-operative Urodynamic Data

<i>Patients</i>	<i>Time from prostatic resection (months)</i>	<i>Voided volume (ml)</i>	<i>Residual volume (ml)</i>	<i>Voiding time (s)</i>	<i>Maximum flow rate (ml/s)</i>	<i>Voiding efficiency (%)</i>
D.H	3	208	0	23	14.1	100
G.W.	9	268	0	30	18.4	100
D.M.	10	152	40	15.2	12.5	80
K.D.	3	220	20	20	15	92
A.I.	4	410	40	33	17.5	92
J.Mc	3	235	0	36	10.9	100
J.R	9	230	0	16	24.6	100
J.P.	3	201	0	20	15	100

in the control and study groups prior to and following removal of outflow tract obstruction. The results are shown in Tables 4 and 5. Prior to operation there was a significant difference in the number of nerves between the 2 groups, with a significantly higher number in the control group ($P < 0.01$). Comparison of the mean muscle areas in the 2 groups showed no statistically significant difference. The innervation index therefore showed a significant reduction in the obstructed group ($P < 0.01$).

Study group. Comparative morphometric studies with the relief of outflow tract obstruction showed an increase in the mean number of nerves in 8 patients and a decrease in 2 (Table 5). Comparison of smooth muscle areas showed no statistically significant alteration. The difference in innervation indices was statistically significant ($P < 0.02$). With relief of outflow tract obstruction the detrusor innervation returned to normal levels, there being no statistically significant difference between innervation indices in the control and non-obstructed groups.

Discussion

Animal studies have shown that with the onset of outflow tract obstruction there are changes in smooth muscle morphology (Uvelius *et al.*, 1984), changes in connective tissue infiltrate (Susset, 1983) and reduction in detrusor innervation (Gosling *et al.*, 1986). Morphological smooth muscle hyperplasia and hypertrophy have not been consistently demonstrated in man (Gosling and Dixon, 1980)

Table 4 Morphometric Data: Control Patients

Patients	Mean no. of nerves	Mean % muscle area	Mean innervation
C.P.	113.5	46	2.88
J.M.	64.5	54	1.15
C.G.	33.9	82	0.4
R.B.	37.4	50	0.8
J.B.	39.3	51	0.87
W.W.	34.2	50.9	0.74
W.M.	8.3	45	0.19
W.W.	101.4	71	1.5
P.Mc.	35.6	50	0.84
H.M.	93.8	70	1.41
J.Mc.	29.1	57	0.5
W.O.	37.8	54	0.71
D.K.	15.5	43	0.38
J.W.	61.9	42	1.44
J.B.	58.5	58	1.03

Table 5 Morphometric Data: Study Patients

Patients	Mean no. of nerves	Mean % muscle area	Mean innervation
<i>Data at prostatectomy</i>			
J.M.	20.4	54.6	0.36
W.P.	16.4	55.1	0.36
G.W.	7.3	65	0.11
K.D.	1.8	50.4	0.04
J.R.	6.8	57.1	0.14
D.M.	15.3	59.5	0.25
A.I.	9.2	78.4	0.12
J.Mc.	1.5	51.9	0.03
D.H.	31.2	56.8	0.56
J.P.	34.6	55.8	0.67
<i>Data after prostatectomy</i>			
J.M.	48.1	47.9	1.37
W.P.	2.2	51.4	0.06
G.W.	22.9	68.8	0.35
K.D.	26.9	50.6	0.58
J.R.	15	52.4	0.63
D.M.	1.9	39.5	0.05
A.I.	44.5	68	0.65
J.Mc.	41.6	77.8	0.54
D.H.	77	55.9	1.47
J.P.	67.2	55.5	1.24

but there is evidence from subsequent morphometric studies that hypertrophy occurs alone (Gilpin *et al.*, 1985). Connective tissue infiltration subsequent to outflow tract obstruction has been seen in the rat model (Uvelius and Mattiasson, 1984) and is known to increase in man with age (Susset *et al.*, 1978).

Against these background morphological changes, morphometric studies on detrusor innervation have been performed which describe a decrease in detrusor innervation with age (Gilpin *et al.*, 1986) and with obstruction (Gosling *et al.*, 1986). The morphometric method used in these assessments compensated for smooth muscle hypertrophy and/or hyperplasia. Despite this attempt to add dilutional factors into nerve counts, this method has been criticised (Meyer and Elbadawi, 1989). In view of this criticism this study made no attempt to describe changes in smooth muscle morphology. Instead, with the application of the Delesse (1847) principle it is possible to comment on the changes in smooth muscle volume between groups.

This study used an immunohistochemical method to identify nerve. PGP 9.5 is a ubiquitous neuronal marker. It is found in neuronal cytoplasm (Doran *et al.*, 1983), in all nerve types (Gulbenkian *et al.*, 1987) and is present throughout the nerve, staining fine varicose nerves not stained with non-specific enolase (Lundberg *et al.*, 1988). Both the

monoclonal and the polyclonal antibody to PGP 9.5 are effective in identifying nerve in sections which have been formalin fixed and paraffin processed (Wilson *et al.*, 1988). This enables historical sections to be stained without loss of immunoreactivity.

The morphometric method used for muscle assessment cannot be used to determine either smooth muscle cell hypertrophy or hyperplasia but gives information about the relative volumes of muscle and connective tissue. In this study there was no statistically significant change in the volume of smooth muscle between the control and study group prior to, and following relief of obstruction; furthermore, there was no change in this parameter in the study group following prostatectomy. It can be argued that this result does not mean that there is no change in individual smooth muscle cells, but rather that if hyperplasia and hypertrophy do occur these changes are insignificant. The absence of statistically significant change in either the smooth muscle or connective tissue components supports the concept of a "real" change in innervation and not one which is simply due to dilutional effects.

This study suggests that there is a decrease in detrusor innervation with outflow tract obstruction compared with controls and that detrusor innervation increases to normal levels in the majority of patients with the relief of outflow tract obstruction. These findings confirm earlier work by Gosling *et al.* (1986) and give credence to their observations that ultrastructurally, although nerve axons were damaged, there was no damage to the cell body, thereby leaving the potential for axonal regeneration. The sample size of this study is too small to draw any further conclusions but it is interesting to speculate that persistence of symptoms following prostatectomy may be caused by failure of the detrusor nerves to regenerate.

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Inhibitory Role of Gamma-amino-butyric Acid in the Rabbit Urinary Bladder

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Summary—Gamma-amino-butyric acid (GABA) is an established inhibitory neurotransmitter in the central nervous system (CNS) and it has also been identified in the bladder. We have investigated in the rabbit the effect of GABA on detrusor activity.

Rabbit detrusor muscle strips were made to contract by electrical stimulation of their autonomic nerves or by the addition of carbachol. The addition of GABA caused substantial inhibition of muscle contraction. GABA acts on 2 classes of receptors—GABA_A and GABA_B. The inhibition was mediated via the GABA_B receptors as its effect was mimicked by baclofen (a GABA_B agonist) and inhibited by 2-hydroxysaclofen (a GABA_B receptor antagonist). Inhibition was not prevented by bicuculline (a GABA_A receptor antagonist). This inhibition may be due to a direct muscle effect since the inhibition, which occurred with carbachol-induced contraction, was not abolished by the addition of tetrodotoxin.

GABA, acting via the GABA_B receptor, produces substantial inhibition of muscle contraction in the rabbit urinary bladder. This raises the possibility of using GABA_B analogues in the treatment of detrusor instability.

It has been known for some time that non-adrenergic, non-cholinergic (NANC) neurotransmission occurs in the urinary bladder. Purinergic transmission can account for up to 60% of detrusor contraction in some species, although its importance in human neurotransmission is uncertain. More recently, it has become clear that there are important inhibitory mechanisms in the bladder. Studies of this NANC neurotransmission may provide an effective pharmacological approach to the management of detrusor instability.

The amino acid, γ -amino-butyric acid (GABA), is an established inhibitory neurotransmitter in the CNS and it has recently been identified in the urinary bladder (Kusunoki *et al.*, 1984). GABA acts on 2 classes of receptors, the GABA_A and GABA_B receptor. These 2 receptors can be distin-

guished by their selective agonists and antagonists. Activation of the GABA_A receptor results in the entry of Cl⁻ ions into nerves, whereas activation of the GABA_B receptor is thought to affect the K⁺ or Ca⁺⁺ channels on nerves or smooth muscle (Bowery, 1989). GABA has been shown to inhibit nerve-mediated contraction of detrusor smooth muscle strips by 2 groups of workers, but the mechanism of action is still unclear. Taniyama *et al.* (1983) presented evidence that GABA inhibited the cholinergic component of electrically induced contraction of guinea-pig bladder muscle strips and that it was mediated via the GABA_A receptor. These workers also demonstrated that GABA inhibited [³H]ACh (acetylcholine) release from cholinergic post-ganglionic nerves via GABA_A receptors (Kusunoki *et al.*, 1984). However, Santicioli *et al.* (1984) investigated the effects of GABA on the electrically induced contractions of rabbit bladder preparations and found that the inhibition was mediated via the GABA_B receptor. They were subsequently able to demonstrate the same findings

in guinea-pig bladder preparations and that GABA inhibited both the cholinergic and NANC component of excitatory transmission (Maggi *et al.*, 1985a, b).

In the presence of these uncertainties of the mechanism of action of GABA, the effects of GABA on nerve-mediated contractions of rabbit urinary bladder strips were investigated.

Materials and Methods

Male Dutch rabbits weighing 800 to 1000 g were killed and the bladder removed and placed in ice cold Krebs' solution. Muscle strips were obtained measuring approximately 8 mm in length and 2 mm in diameter. They were stored for a maximum of 20 h at 4°C in oxygenated Krebs' solution before their use. The strips were suspended in a superfusion chamber (capacity 0.2 ml) of the Brading and Sibley design (1983) and superfused with Krebs' solution (NaCl 124; KCl 5; MgCl₂ 1.3; NaHCO₃ 26; CaCl₂ 0.8; KH₂PO₄ 1.4 and Glucose 10 [mM] continually gassed with 95% O₂ and 5% CO₂) at 37°C and at 1 ml/min. A loading tension of 0.5 g was applied and the strips were allowed to equilibrate for 1 h. The muscle strips were then stimulated with electrical field stimulation at a constant frequency to ensure that stable reproducible contractions were obtained.

Nerve-mediated contractions were obtained using electrical field stimulation by means of 2 platinum electrodes. The stimulation parameters used (3-s trains of 30 V square wave pulses with 0.2-ms pulse width in the range 1–40 Hz) were shown to stimulate selectively the intramural nerves rather than the smooth muscles in the strips; this was confirmed by abolishing the contractions with the addition of tetrodotoxin (TTX) (1×10^{-7} M). Frequency response curves were constructed in the range of 1 to 40 Hz with stimuli repeated at 4-min intervals and then repeated in the presence of GABA and its analogues. Dose response curves to inhibitors were constructed by using a constant frequency of 10 Hz and taking the mean of 4 responses at each drug concentration and expressing the result as a percentage inhibition of the control contraction. A 5-min interval was allowed for each change of solution before electrical field stimulation was applied.

Carbachol-mediated muscle contractions were obtained by adding the concentration of carbachol (5×10^{-6} M) to the superfusion chamber and exposing the tissue for 10 s. The effects of GABA and

baclofen on carbachol-mediated contractions were then observed by superfusing the tissue with the concentration of the drugs dissolved in Krebs' solution.

Statistical analysis was performed using Student's *t* test. Comparisons of the dose response curves were performed by computer curve fitting using a Hill equation. The EC₅₀ (the stimulus required to produce a contraction which is 50% of the maximal response) and the maximum response were obtained from the computer estimates and compared between 2 groups with Student's *t* test. The curve fitting programme was not suitable for the frequency response curves and comparisons of corresponding points on the curve were made with the *t* test. Significance levels unless stated are $P < 0.05$.

The drugs used were GABA; ($\pm$) baclofen (GABA_B agonist); muscimol (GABA_A agonist); 2-hydroxysaclofen (GABA_B antagonist); bicuculline methobromide (GABA_A antagonist); carbachol and tetrodotoxin. All drugs were obtained from Sigma Chemicals except for 2-hydroxysaclofen, which was obtained from Tocris Neuramin.

Results

Effects of GABA on nerve-mediated muscle contractions

GABA produced a concentration-dependent inhibition of muscle contraction induced by electrical field stimulation at 10 Hz. The maximum inhibition was $32.5 (\pm 1.9)\%$ with an EC₅₀ of $3.42 (\pm 0.69) \times 10^{-6}$ M ($n = 7$ strips) (Fig. 1A). GABA also caused a significant right shift of the frequency response curve ($n = 15$) (Fig. 2A).

Effects of GABA agonists

($\pm$) baclofen also produced a concentration-dependent inhibition with a maximum inhibition of $26.5 (\pm 1.58)\%$ and an EC₅₀ of $7.26 (\pm 1.2) \times 10^{-6}$ M ($n = 8$) (Fig. 1B), and caused a significant inhibitory effect on the frequency response curve ($n = 13$) (Fig. 2B). Muscimol, the GABA_A receptor agonist, in a concentration range of 1×10^{-8} to 1×10^{-5} M, had no inhibitory effect ($n = 5$).

Effects of antagonists on GABA inhibition

The addition of the GABA_B antagonist, 2-hydroxysaclofen (1×10^{-5} M), caused a significant antagonism of the inhibition produced by GABA, with an increase of the EC₅₀ to $7.82 (\pm 0.62) \times 10^{-6}$ M.

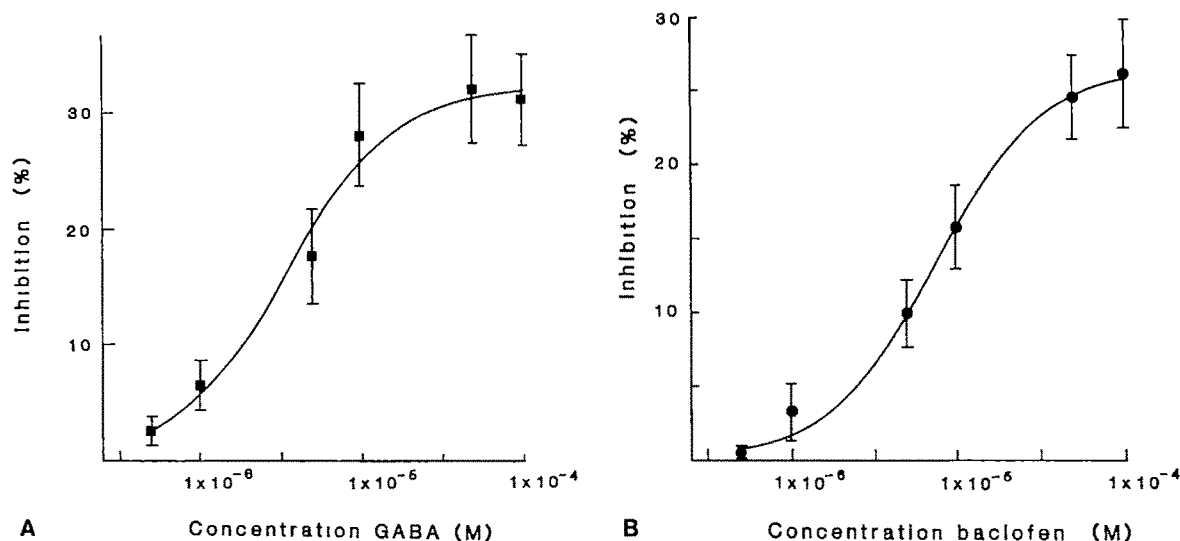


Fig. 1 Dose inhibition curves for (A) GABA ($n=7$) (■) and for (B) (±) baclofen ($n=8$) (●). Results expressed as the percentage inhibition of muscle contractions by electrical field stimulation of controls (10 Hz, 0.2 ms pulse width, 30 V for 3 s). Values are means ($\pm$ SEM). Computer generated best fit curves are shown.

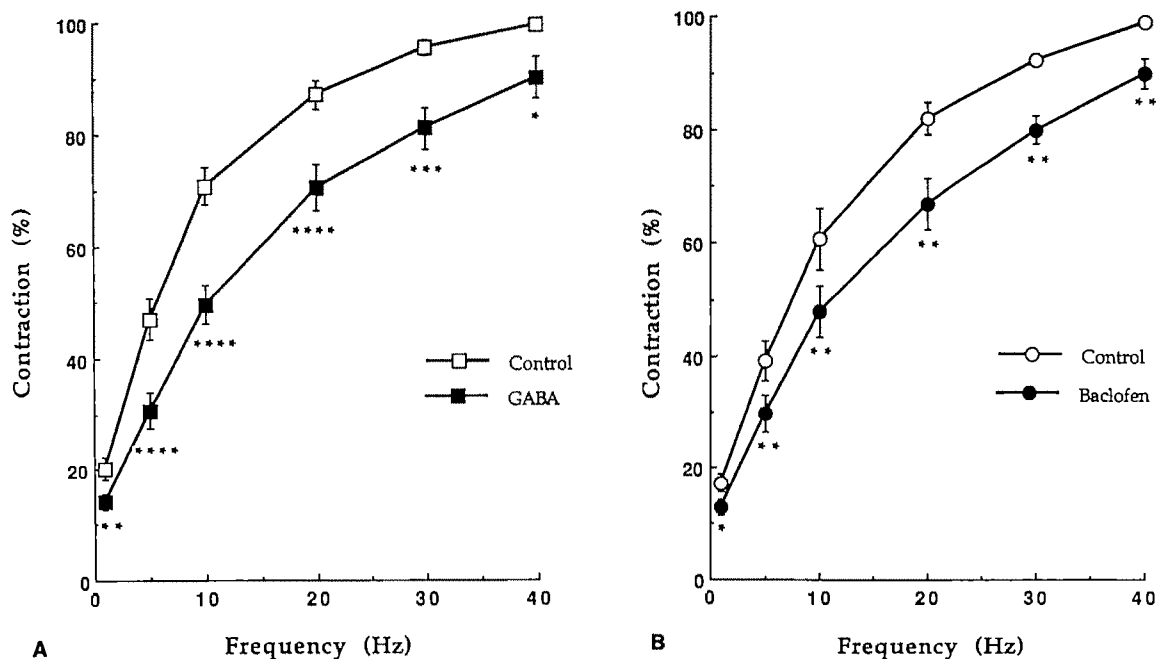


Fig. 2 Frequency response curves for muscle strips with the addition of 1×10^{-5} M GABA (A) or with the addition of 1×10^{-4} M baclofen (B). Each point represents the mean $\pm$ SEM of values. Comparisons of the values from the control values with the t test: * $P < 0.05$; ** $P < 0.005$; *** $P < 0.001$; **** $P < 0.0005$.

($n=8$) ($P < 0.0005$) and no significant difference in the maximum response. The addition of bicuculline (1×10^{-5} M) to GABA produced no significant change in the EC_{50} ($3.85 \pm 0.39 \times 10^{-6}$ M) but caused a significant increase in the maximum response ($P < 0.0025$) ($n=6$) (Fig. 3).

Effects on carbachol-induced muscle contractions

GABA produced a dose-dependent inhibition of carbachol (5×10^{-6} M) induced muscle contraction in 10 strips (Fig. 4A), but no inhibition was seen in 6 strips. In 4 experiments, the addition of TTX ($1 \times$

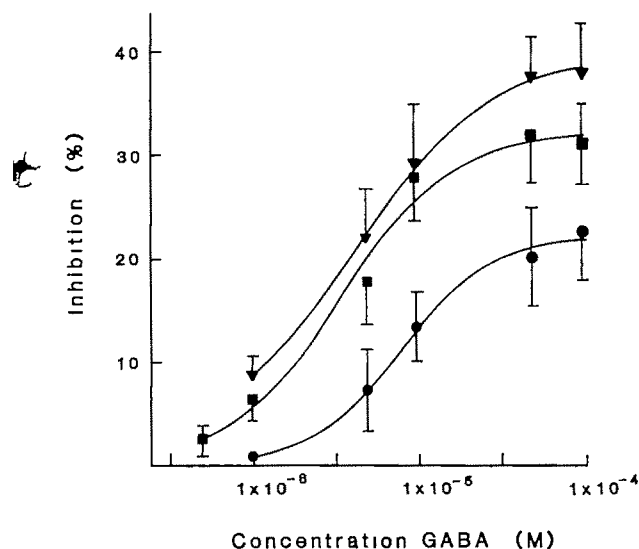


Fig. 3 Dose inhibition curve for GABA alone ($n=7$) (■), with the addition of 2-hydroxysaclofen ($n=8$) (●) and with the addition of bicuculline ($n=6$) (▼). Values are means ($\pm$ SEM). Computer generated best fit curves are shown. See text for EC_{50} values.

10^{-7} M) did not abolish the inhibition produced by 1×10^{-4} M dose of GABA. ($\pm$) baclofen was also able to inhibit the muscle contraction in 6 strips, although the effect was not seen in 3 strips (Fig. 4B).

Discussion

These findings demonstrate that the inhibitory effect of GABA on muscle strip contraction induced by electrical field stimulation of the intramural

nerves is mediated by the $GABA_B$ receptor. This conclusion stems from the finding that the inhibitory actions are mimicked by ($\pm$) baclofen, a $GABA_B$ receptor agonist but not by muscimol, the $GABA_A$ receptor agonist. In addition, the inhibitory actions can be reversed by the $GABA_B$ receptor antagonist, 2-hydroxysaclofen, but not by bicuculline, a $GABA_A$ receptor antagonist. These results support the findings of Santicioli *et al.* (1984) that in the rabbit detrusor, the inhibitory actions of GABA are mediated by the $GABA_B$ receptor.

The early experiments on the guinea-pig urinary bladder indicated that the inhibition of GABA was mediated through the $GABA_A$ receptor (Taniyama *et al.*, 1983; Kusunoki *et al.*, 1984). However, Maggi *et al.* (1985a,b) considered the major inhibitory actions to be mediated through $GABA_B$ receptors.

Erdo *et al.* (1989) used [^3H]-muscimol to identify $GABA_A$ receptor sites in the guinea-pig bladder and found a large number of receptors in the bladder base and urethra, with no specific binding in the body of the bladder. However, measurements of tissue levels of GABA in guinea-pig bladder by Kusunoki *et al.* (1984) found the highest concentration in the body of the bladder.

Attempts to localise the tissue site of action of GABA in the bladder have proved equally confusing. Kusunoki *et al.* (1984) attributed the inhibitory actions of GABA to its capacity to reduce acetylcholine release from post-ganglionic parasympathetic nerve fibres, through $GABA_A$ receptors. Maggi *et al.* (1985a,b) considered on the other hand that these inhibitory pre-synaptic receptors were of the $GABA_B$ type, and that stimulation of $GABA_A$ receptors produced potentiation of contraction.

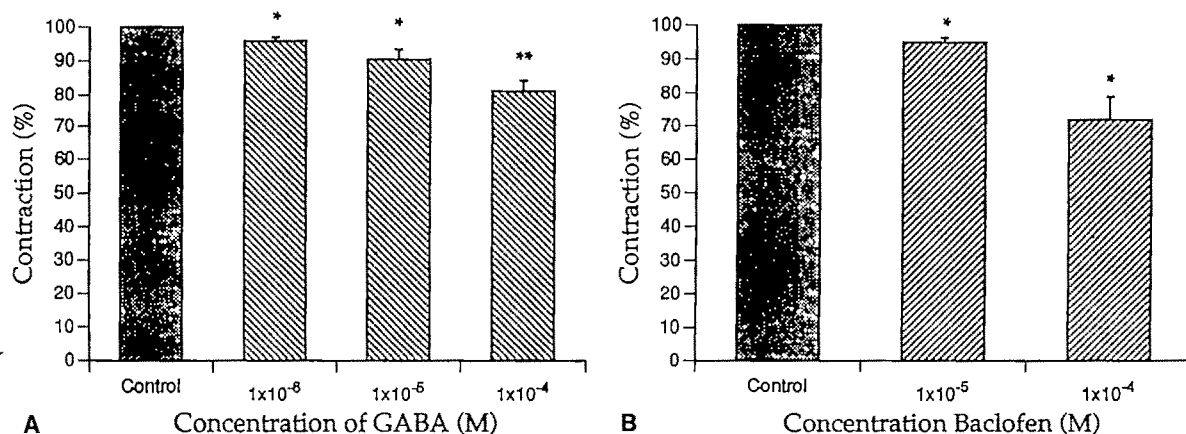


Fig. 4 Concentration-dependent inhibition of carbachol 5×10^{-6} M induced muscle contractions by the addition of (A) GABA ($n=10$) and by (B) baclofen ($n=6$). Values are means ($\pm$ SEM). Comparison of the values from the control values with the t test: * $P < 0.005$; ** $P < 0.001$.

These authors also showed that GABA caused inhibition of ACh-induced muscle contraction in guinea-pig bladder but they concluded that this action was mediated through some neurogenic mechanism.

Our own finding that both GABA and baclofen inhibited carbachol-induced muscle contractions and that these effects were not inhibited by TTX (1×10^{-7} M) is best explained if GABA has a direct effect on detrusor smooth muscle cells through GABA_B receptors. Although the improvement seen in patients with idiopathic detrusor instability (Taylor and Bates, 1979), and with neurogenic voiding disturbances (Haubensack, 1977) following baclofen treatment, has been attributed to its actions on the spinal cord, it could equally well be explained by its actions on the bladder itself. The failure of baclofen and GABA sometimes to produce direct inhibition of bladder smooth muscle cells suggests that GABA may have a more complex action on bladder function than the present experiments indicate and we are presently extending our investigations in this area.

In summary, GABA inhibits contraction of bladder muscle strips when they are made to contract by electrical stimulation of their autonomic nerves. This inhibition is mediated via the GABA_B receptors, though our experiments do not exclude other GABA-mediated actions on bladder function.

Acknowledgement

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Agreement between Clinical Methods of Measurement of Urinary Frequency and Functional Bladder Capacity

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Summary—We assessed the agreement between 2 methods of data gathering of particular interest in urology: patient questionnaire and examination *vs.* frequency-volume charts. One hundred consecutive patients consulting our out-patient clinic were chosen for this study; 88 completed the study. Urinary frequency and bladder capacity were evaluated in each patient by using the above methods. The agreement between different methods of measurement was assessed by determining whether the 2 methods were interchangeable, a condition occurring if results of both methods fall within predetermined limits of variability. The results showed poor agreement between subjectively estimated urinary frequency and chart-determined urinary frequency. Moreover, different methods of measuring bladder capacity (endoscopic *vs.* chart) gave different results. Since chart-determined data are probably a more valid indication of urinary habits, we suggest that frequency-volume charts should be used more often in the investigation and follow-up of patients with micturition disorders.

A thorough medical history and a complete physical examination are the mainstays of medical practice. Parameters such as urinary frequency and bladder capacity are of particular interest in urology. Urinary frequency is usually determined by questioning patients, and bladder filling during cystoscopic examination is used to assess bladder capacity (cystoscopic bladder capacity). Only a few studies have tested the reliability of such methods (George *et al.*, 1981; Abrams *et al.*, 1983; George, 1986).

The data gathered by questioning patients and from cystoscopic examination can be compared with similar data from a frequency-volume chart. Both urinary frequency habits and average voided volume (functional bladder capacity) can be evaluated by using these charts.

In this study we assessed the agreement between these 2 methods of data gathering (patient questionnaire and examination *vs.* frequency-volume charts).

Patients and Methods

One hundred consecutive patients who consulted our out-patient clinic were chosen for this study. Patients were selected if it was their first visit to the clinic and if they required a cystoscopic examination because of the presenting complaint (haematuria, incontinence, *etc.*).

During their first visit the patients were questioned about their usual diurnal and nocturnal urinary frequency over the last 6 months. They were then asked to fill out a frequency-volume chart at home by noting the time and volume of each micturition for 7 consecutive days and nights. The patients determined their micturition volumes by urinating in a quantitative container. The detailed instructions were printed on the back of the chart, with illustrative examples. An episode of urinary incontinence or an unrecorded micturition volume were also noted. Once completed, the urinary frequency-volume chart was returned to us, and the patient was then evaluated endoscopically. During cystoscopy, the bladder capacity was determined. This was done by asking the patient to indicate when he or she felt a strong desire to void;

the bladder volume at this point was recorded as being the cystoscopic bladder capacity. All cystoscopic examinations were performed by the same physician. Post-voiding residual urine was noted.

From each frequency-volume chart filled out by the patient, the mean daytime, nocturnal, and 24-hour frequencies were estimated. The average diurnal and nocturnal volumes of each micturition were also calculated.

We then compared urinary frequency (diurnal and nocturnal) as determined by patient questionnaire with the results obtained on the frequency-volume chart.

Statistical analysis

The mean and standard deviation were calculated for each of the 7 measurements (diurnal and nocturnal urinary frequency from patient questionnaire and from frequency-volume chart, diurnal and nocturnal functional bladder capacity from frequency-volume chart, and bladder capacity from cystoscopic examination). The mean differences (d) in urinary frequency measurements obtained from patient questionnaire *vs.* frequency-volume chart were estimated. Mean differences between bladder capacity measurements (cystoscopic examination *vs.* frequency-volume chart) were also estimated along with the standard deviations (s) of the differences. In this study, agreement between the different measurements was assessed according to

a method suggested by Bland and Altman (1986) which states that 2 measurement methods (*e.g.* urinary capacity from patient questionnaire and from frequency-volume chart) are interchangeable provided that differences within $d \pm 2s$ are not clinically important. The calculations from $d \pm 2s$ are referred to as "limits of agreement".

If the scatter of the differences between measure "a" (patient questionnaire) and measure "b" (frequency-volume chart) increases as the average of the 2 measures increases, then the method, although still applicable, has a drawback: the limits of agreement will be wider apart than necessary for small values of the urinary frequency and narrower for large frequencies. Logarithmic transformation of the data will often solve this problem.

Results

Mean diurnal and nocturnal urinary frequencies were very similar as determined by both methods. The mean difference between the 2 methods for diurnal frequency was 1.27 (95% confidence limits (CL), 0.04–2.13), indicating that the reported frequency from the patient questionnaire was higher on average than that from the frequency-volume chart. The limits of agreement suggested that the diurnal urinary frequency elicited from patient questionnaire may be 6 times per day lower or 9 times per day higher than that estimated by

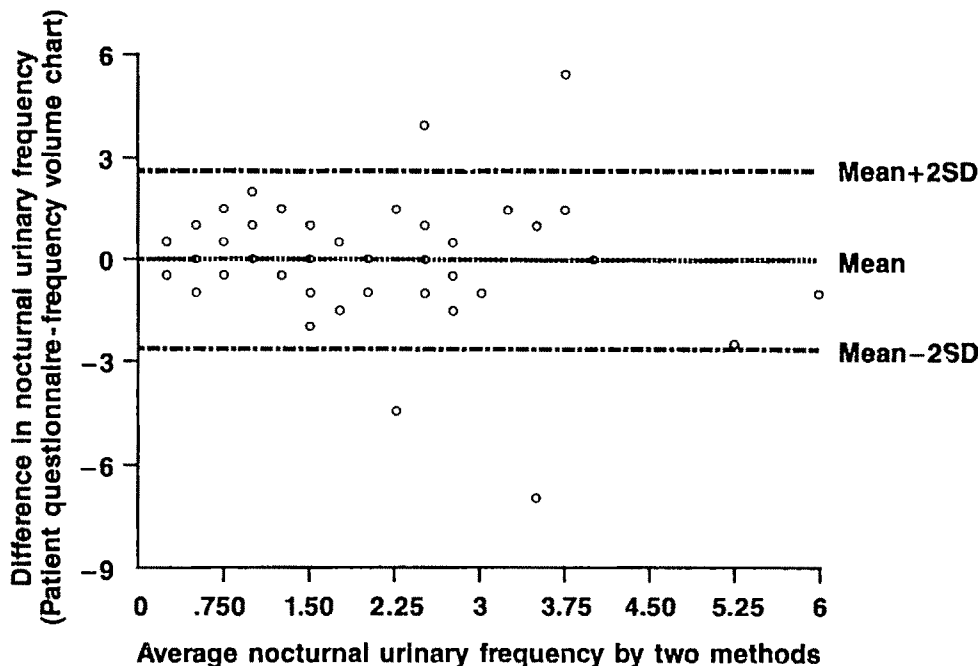


Fig. 1. Difference against mean for nocturnal urinary frequency

the frequency-volume chart: acceptable limits for urinary frequency reported in patient questionnaire would be within 2 times lower or higher than that measured by the frequency-volume chart. There was a significant correlation between the difference and the average of the 2 diurnal measures which was not corrected by a logarithmic transformation of the data: the questionnaire showed lower frequencies than the frequency-volume chart for mean values which were 7 or below, and higher frequencies for mean values greater than 7. In comparison, the mean differences between the 2 methods for nocturnal frequency was zero (95% CL, -0.31 to 0.31). There was no correlation between the difference and the mean of the two measures (Fig. 1): the limits of agreement suggested that reported nocturnal frequency from the patient questionnaire may be 3 times per night lower or higher than that from the frequency-volume chart. These limits are beyond those already suggested as acceptable.

The average cystoscopic bladder capacity was 382.28 ml (± 149.1). Using the frequency-volume chart method, the average diurnal bladder capacity was 175.56 ml (± 64.29), and the average nocturnal bladder capacity was 232.5 ml (± 129.64).

The mean difference between cystoscopic examination and diurnal frequency-volume chart was 205.85 (95% CL, 177.78-233.92). There was a

significant correlation between the difference and the mean of the 2 methods (Fig. 2) which was corrected by using a logarithmic transformation (Fig. 3). The mean difference was 0.77 on the log scale, and the limits of agreement were -0.03 and 1.58. After logarithmic transformation, the latter showed that for about 95% of cases, cystoscopy will yield values between 0.96 and 4.87 times those from the diurnal frequency-volume chart. Thus the cystoscopy may differ from the frequency-volume chart measurement by 4% below to 387% above. Finally, cystoscopy was compared with nocturnal frequency-volume chart. The mean difference between the 2 measures was 149.83 (95% CL, 116.58-183.07). There was no correlation between the difference and the mean of the 2 measures. Limits of agreement suggested that cystoscopy measurement may be 163.59 ml lower and 463.25 higher than nocturnal frequency-volume chart measurement. Acceptable limits would be within plus or minus 100 ml.

Discussion

In this study we tested the agreement between 2 methods of clinical assessment available to the urologist (patient questionnaire and physical examination *vs.* frequency-volume chart). The results from our analysis of 88 patients revealed a poor

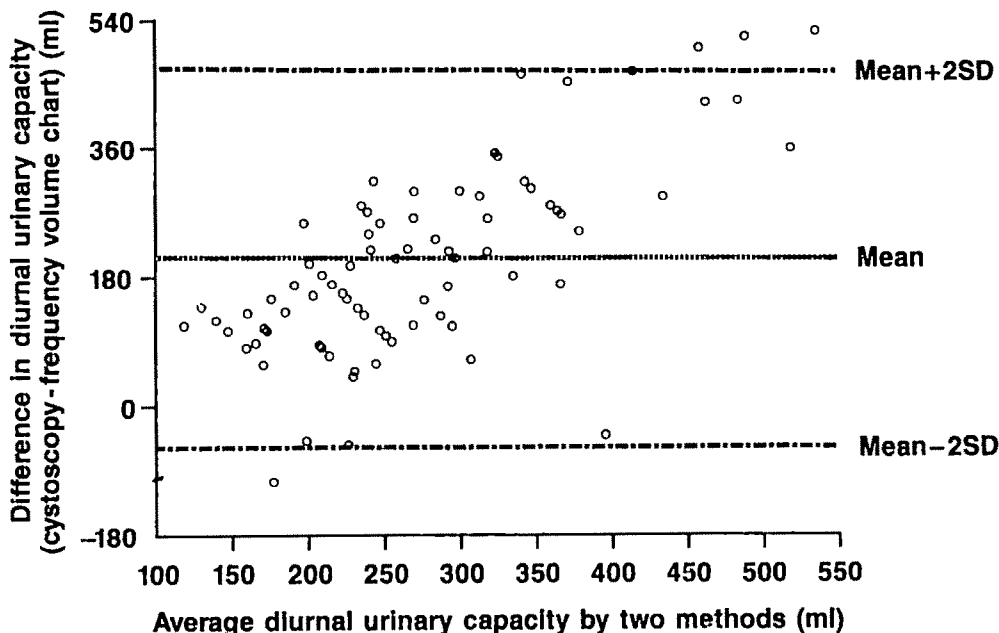


Fig. 2. Difference against mean for diurnal urinary capacity

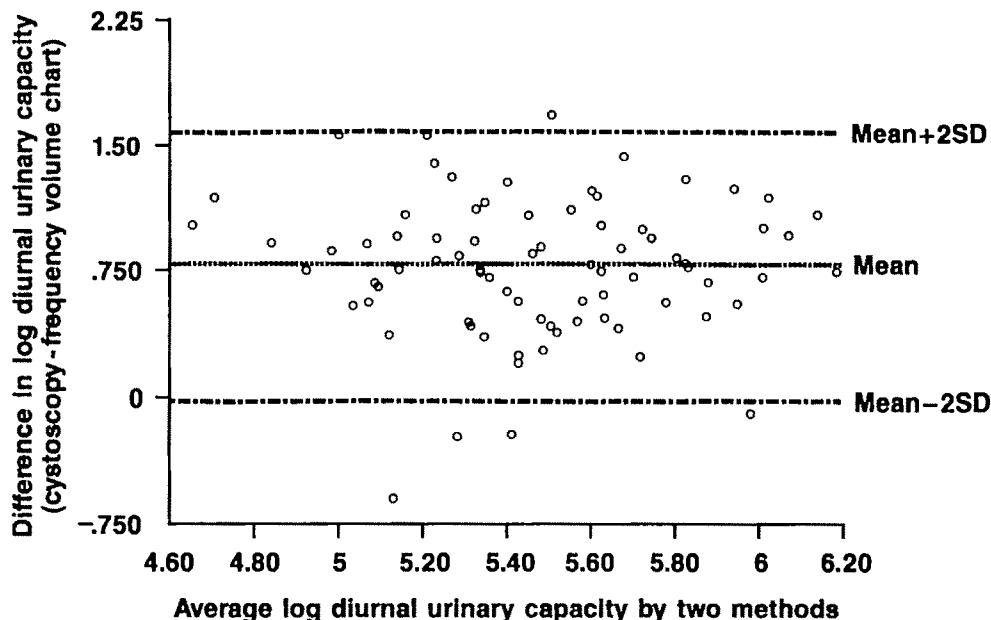


Fig. 3 Data of Figure 2 after logarithmic transformation

agreement between subjectively estimated urinary frequency (diurnal and nocturnal) and chart-determined urinary frequency. We cannot consider these 2 methods of data gathering as interchangeable.

Bladder capacity was not identical when determined by 2 methods of assessment (endoscopic *vs.* chart). Endoscopically determined bladder capacity ($382.38 \text{ ml} \pm 149.1$) was higher than either diurnal or nocturnal bladder capacities as determined by frequency-volume chart. These results are at variance with those reported by George and Lewis (1983) who found that maximum cystometric capacity is only about 60% of the average functional capacity. However, our data are very similar to the data reported by Diokno *et al.* (1987) who compared self-reported voided volume with cystometric bladder capacity in 200 elderly women. In their study, the mean self-reported voided volume was 194 ml while the mean cystometric bladder capacity was 377 ml. Thus both Diokno's and our study suggest little agreement between cystoscopic and chart-determined bladder capacity. The chart-determined bladder capacity was very similar to the bladder capacity of patients evaluated endoscopically when these patients reported their first desire to void (Diokno *et al.*, 1987).

It is tempting to speculate that patients may void in everyday life at their "first desire to void" volume

as determined by the frequency-volume chart. Endoscopically determined bladder capacity may represent the absolute maximum capacity, which is not frequently used by patients in everyday life.

In summary, our study suggests a poor agreement between patient questioning and chart-determined urinary frequency. These 2 methods may not be considered interchangeable as regards urinary frequency. Also, there is a very poor agreement between endoscopically determined and chart-determined bladder volume, the former being approximately twice the value of the latter. Since chart-determined bladder capacity is probably a more valid indication of urinary habits, we suggest that frequency-volume charts be used more often in the investigation and follow-up of patients with micturition disorders. Frequency-volume charts should be particularly useful in evaluating functional bladder capacity in patients with diseases which reduce bladder volume (e.g. interstitial cystitis) and in their post-treatment follow-up period (e.g. bladder distension or enterocystoplasty).

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P25890

Endoscopic Implantation of Collagen (GAX) for the Treatment of Urinary Incontinence

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Summary—Sixteen women whose ages ranged from 42 to 73 years (mean 57) and 2 men, aged 76 and 80 years respectively, were treated for urinary stress incontinence with transurethral implantation of submucosal glutaraldehyde cross-linked collagen (GAX); 15 females had had several continence operations previously and 1 female was totally incontinent following low anterior resection of the sigmoid colon for cancer. All but 2 patients received 8 ml GAX in a single operative session under general anaesthesia. Before implantation, patients underwent urodynamic evaluation, cystoscopy, urinary stress test and the two-thirds capacity pad weighing test. Post-operative evaluations were carried out after 3, 6 and 9 months and included urinary flow rate, urine analysis, residual urine determination and the two-thirds pad weighing test. The results were encouraging.

After 3 months, 8/18 patients were cured, 7/18 had improved and 3/18 had failed to respond. Nine months post-operatively, 7 patients were still continent, 8 had improved and 3 remained unchanged. One of the improved group had a reinjection 18 months post-operatively and has been continent since then.

We feel that GAX collagen injection is a safe and easy method for the treatment of urinary stress incontinence; it has no observable or measurable morbidity.

Since 1938, the endoscopic injection of agents into urethral tissues has been used to add urethral bulk, to narrow the urethra and to increase urethral resistance as an alternative to classical surgical approaches in the management of urinary stress incontinence (Quackels, 1955; Sachse, 1963). Berg (1973) and Politano *et al.* (1974) reported that Teflon paste could be injected into the urinary sphincter in incontinent female patients in order to improve continence. The endoscopic implantation of Teflon paste (EITP) into the sphincter area was proposed as an alternative to major surgery or artificial sphincter implantation. EITP was offered to incontinent patients with previous unsuccessful operations, scarring or radiation therapy who required further reconstruction. This treatment seemed extremely simple and first reports were promising. The lack of long-term follow-up and

adverse local and peripheral reactions reduced the amount of support for the procedure.

Submucosal extrusion of the polytef paste either alone or combined with distant migration of the Teflon from the site of injection has been demonstrated by Malizia *et al.* (1984). Distant granulomas have been reported in liver, lung and spleen.

Since cross-linked collagen (GAX) has been used intradermally to correct facial and bodily defects, without systemic or local reaction, it appeared to be the ideal substance to correct defects in the urinary sphincter. Subureteric collagen implantation has also been used to treat vesicoureteric reflux (Lipsky, 1990) and male stress incontinence (Shortliffe *et al.*, 1989).

Histological evaluation of ureteric and vesical injection sites after failed endoscopic antireflux procedures revealed no significant foreign body giant cell reaction in response to the implanted collagen after 12 and 19 months (Leonard *et al.*, 1990).

Our experience with this substance in treating male and female incontinence is described.

Patients and Methods

Between 1987 and 1989, 18 of 200 neurourologically and urodynamically evaluated incontinent patients were deemed candidates for GAX injection therapy. The group included 16 women, ranging in age from 42 to 73 years (mean 57), and 2 men aged 76 and 80 years. All had failed to respond to other forms of management or surgical treatment of incontinence.

Incontinence was graded clinically on a scale from 0 to III and objectively measured by the two-thirds capacity pad weighing test (Kralj, 1989), the simplified but reliable modification of the original pad weighing test proposed by the International Continence Society. Uroflowmetry, cystoscopy, nephrosonography and GAX intradermal skin testing ensured that the patients had no underlying urological pathology or local hypersensitivity to GAX.

Stress incontinence in the 2 male patients developed after prostatectomy for benign hyperplasia. All but 1 of the female patients had had a vaginal hysterectomy and vaginal repair with some form of suspension operation before treatment with GAX (Table 1).

Cystometry, urinary flow rate, residual urine determination and pad weighing tests were performed pre-operatively. Three, 6 and 9 months after treatment, residual urine determination, urinary flow rate and the two-thirds pad weighing test were repeated.

Cystometry was performed through an 8 F double-lumen urethral catheter with slow drip saline infusion. Patients with detrusor instability whose spontaneous detrusor contractions exceeded 15 cm H₂O were excluded, as were patients with non-compliant bladders (*i.e.* bladders with a gradual increase >40 cm H₂O during the filling phase of

the cystogram). To test the urinary flow rate the bladder was filled through a single-lumen catheter with warm saline up to two-thirds of the maximum capacity; the catheter was then removed and patients were asked to urinate. A similar procedure was used for the control studies.

The two-thirds capacity pad weighing test was performed after measuring the maximum bladder capacity by cystometry. The bladder was emptied by catheterisation and then filled with warm saline to two-thirds of its total capacity. Patients were then asked to perform the following timed, standardised exercises:

- (1) Walking and climbing steps for 30 min.
- (2) Abdominal straining-10 vigorous coughs.
- (3) Jogging or simply lifting the knees while standing for 1 min.
- (4) Ten deep knee bends.
- (5) Washing the hands in cold running water for 1 min.

The weight of the pad was measured either after each of these 5 steps or at the end of the exercises if there was very little urine loss.

Each patient underwent cystoscopy and urine culture pre-operatively; 120 mg gentamicin were given intramuscularly before the GAX injection. Under general anaesthesia the urethra and bladder were visualised and the bladder was filled cystoscopically. A percutaneous 12 F suprapubic catheter was placed in the bladder and its location verified endoscopically. This catheter drained the bladder throughout the implantation procedure and was removed 2 to 4 days after injection. The 21 F cystoscope was then used to visualise the membranous and prostatic urethra and the bladder neck.

Glutaraldehyde cross-linked collagen was injected into the area of the sphincter transurethrally through an Angiomed 5 F, 42-cm needle under endoscopic control. Each patient received a total of 8 ml GAX in 1-ml increments at the 3, 6, 9 and 12 o'clock positions circumferentially. This formed

Table 1 Details of Patients

	Prostatectomy	Low anterior resection	Hysterectomy, vaginal repair (Raz, Stamey)	Hysterectomy, vaginal repair, sling	Hysterectomy, vaginal repair, sling (Raz, Stamey)	Hysterectomy, vaginal repair, sling (Raz, Stamey) Teflon
Cured	1	—	2	2	3	—
Improved	—	1	3	—	2	1
Failed	1	—	1	—	1	—
Total	2	1	6	2	6	1

2 rings before and around the sphincter. Once the lumen was occluded during flow, the injections were stopped and the cystoscope was not inserted beyond the area of injection again.

Patients were hospitalised until micturition without residual urine was obtained, usually 4 to 5 days after injection. All had bedrest for 1 day, the suprapubic catheter was removed 3 to 4 days post-operatively and they were discharged from hospital the following day. No persistent urinary retention occurred. Two patients required a second session 4 and 18 months later.

Results

In 3 patients the collagen implant was a complete failure. One male had total urinary incontinence after transvesical prostatectomy and 1 of the females had remained incontinent following several incontinence operations complicated by severance of the urethral musculature and a urethral fistula. In these 2 patients we saw no prospect of improvement by repeat injections. The third failure was a patient who had undergone hysterectomy plus vaginal repair; 2 years later she had transurethral resection of the bladder neck following urinary retention, followed by 2 bladder neck suspensions and finally 2 GAX injections without success.

The second reinjection was performed after 18 months. The patient was not satisfied with her improvement after the first session and regained complete continence after reinjection.

The remaining patients, 1 man and 14 women, were cured or improved by 1 GAX injection session, according to the two-thirds capacity pad weighing test.

Follow-up ranged from 10 to 22 months (mean 15). Patients were routinely evaluated with urine culture, urine analysis and assessment of residual urine. Re-evaluation took place 10 days after discharge from hospital. In no case was residual urine recorded. Urinary infection, when detected, was treated by appropriate antibiotics.

Three months after the operation 8 patients were totally continent, 7 had improved and 3 showed no

improvement. Nine months post-operatively, 7 patients remained completely dry and continent. 8 continued to improve and 3 were unchanged (Table 2). In 2 cases we performed a second session, 1 of which was successful. This reinjection was done recently, so that 8/18 patients are now completely continent.

When incontinence did recur, it took place between 3 and 5 months after GAX injection therapy, not later.

Clinically, 8 patients reported significant improvement at 3 months, and the two-thirds pad weighing test objectively demonstrated continence. In 7 patients this test dropped from 47.2% (percentage of urine loss) to 15.8% post-operatively, with little change 9 months after operation (13.8%). Three patients derived no benefit from the procedure; they had a 55% urine loss pre-operatively and showed no change after 3 and 9 months (Table 3).

The pre-operative maximum urinary flow rate showed a mean value of 23 ml/s (range 6–66). Three and 6 months post-operatively the maximum rate showed no significant change (mean 20.7 ml/s; range 9.6–48).

Discussion

Urinary continence is normally achieved by 3 main factors:

- (1) Compression of the abdominal part of the urethra by elevation, during abdominal straining.
- (2) Intrinsic smooth muscle contraction in the posterior urethra.
- (3) The inner softness, which is produced by the submucosal venous plexus, elastic elements of the connective tissue and the epithelium of the urethra.

While most continence operations involve suspension of the posterior bladder and urethra, the effect of implantation therapy is to create a tighter sealing of the inner softness.

In 1973, the periurethral injection of polytef (Teflon) for stress incontinence was greeted with enthusiasm. Of concern were studies demonstrating migration of the polytetrafluoroethylene particles from the site of injection and granuloma formation (Malizia *et al.*, 1984). Glutaraldehyde cross-linked collagen does not have these disadvantages. It has been widely used in plastic surgery to correct bodily defects, and in paediatric surgery to treat vesico-ureteric reflux (Lipsky, 1990) without ill effects. These findings suggest that bovine collagen im-

Table 2 Post-operative Results

	At 3 months No.	At 9 months No.
Cured	8	7
Improved	7	8
Failed	3	3

Table 3 Pad Test; Urine Loss (percentage)

	Before operation (%)		3 months post-operatively (%)		9 months post-operatively (%)	
	Range		Range		Range	
Cured	41.8	1.7-98	0		0	
Improved	47.2	12-98	15.8	1-42	13.8	1-42
Failed	55.0	10-100	57.5	15-100		100

Mean follow-up 15 months (range 10-22)

plants can safely be used to treat male and female stress incontinence.

This study has shown that GAX may be injected into the human urinary tract without apparent morbidity. The periurethral injection improved urinary incontinence in 15 of 18 patients (an overall success rate of 83% after 9 months).

The procedure is easy to perform, has no morbidity, and no allergic responses were seen. It can be repeated at any time. Longer follow-up in a larger number of patients is necessary to determine its long-term stability and the degree of inflammatory change engendered several years after injection. Distal migration or resorption was not observed in our patients after a mean observation time of 15 months.

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Transurethral Polytef Injection for Post-prostatectomy Urinary Incontinence

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Summary—This report deals with 720 incontinent males injected with Polytef paste. In all cases the incontinence resulted from some form of prostatic surgery. All patients had been incontinent for at least 1 year. Approximately 88% of patients incontinent from transurethral resection (TURP) were cured or improved; 74% of patients undergoing prostatectomy were improved, and approximately 67% of patients incontinent after radical prostatectomy were cured or improved. No major complications or clinical evidence of particle migration were observed. Our 20 plus years' experience with Polytef paste has shown it to be a safe and effective method for the treatment of post-operative male incontinence, with a high success rate.

Urinary incontinence continues to be a major unresolved problem despite the many surgical repairs to correct the condition. Pharmacological manipulation has not always been successful. It has been estimated that some 10 to 15 million people in the USA alone are troubled with incontinence of some degree. Incontinence presents a major nursing problem in elderly patients, many of whom are physically unable to undergo a more major or complicated surgical procedure. It is in this group of patients, in particular, that a simple method is needed whereby some compatible substance can be injected at the bladder neck or along the urethra to increase urethral resistance to urine outflow. Such procedures can be performed on an ambulatory basis, under minimal general or local anaesthesia. They also have the advantage that they can be repeated, if necessary, without the patient undergoing a major surgical intervention, if the first injection has failed.

Quackles (1955) described the injection of parafin perineally, in an effort to compress the urethra. Sachse (1963) injected a sclerosing agent in the urethra with some success, but pulmonary emboli were encountered. Arnold (1962) injected Teflon (polytetrafluoroethylene) particles into the vocal

cords for rehabilitation of paralytic dysphonia. This suggested the possibility of its use in the urethra for reinforcing the damaged external sphincter. Preliminary injections were done in the urethra of 6 female dogs to study the tissue reaction and to measure outflow resistance. There was minimal tissue reaction and urethral pressure studies showed an increase immediately after surgery, but there was a return to pre-injection levels 3 weeks later.

Politano *et al.* (1973, 1974) began a study injecting Polytef paste (Teflon) periurethrally in 1964. Initially, these injections were done through the perineum and the paste injected around the region of the external sphincter. Since the mid 1970s, when instruments became available for transurethral injection, the majority have been done in this manner. Our early results were encouraging but not consistent. We were unsure of the quantity to inject and there was difficulty in getting the paste in the correct area. Time, experience and proper equipment have helped to resolve these problems. Our results have steadily improved.

Since the beginning of this study, we have injected about 1000 patients. We reported on our experience with 500 males at the 1989 A.U.A. meeting. These were patients incontinent from prostate surgery. All had been incontinent for at least 1 year. They received an average of 1.4

injections, each injection containing about 18 ml of paste. Approximately 88% of the patients who were incontinent following TURP were dry or improved; 74% of those treated by open prostatectomy were cured or improved, and 67% of those who had undergone radical prostatectomy were cured or improved.

Complications were few and minor. There were 3 perineal abscesses in this group, all of which occurred in patients who were injected perineally and required incision and drainage. All of these patients were diabetics.

Patients and Methods

We reviewed the records of 720 patients who had received periurethral Polytef paste injections for urinary incontinence secondary to prostatectomy. From 1964 to 1978, periurethral injections were performed transperineally and we have described this technique elsewhere (Politano *et al.*, 1973, 1974).

Since 1978, injections have been performed cystoscopically following the development of new instruments by Storz and Wolf (Kaufman *et al.*, 1984). The external sphincter area is identified and the paste is injected under direct vision. The sphincter is perforated with the needle and several ml of paste injected. The needle is moved circumferentially around the sphincter until approximately 10 to 20 ml of the paste have been injected and the sphincteric area has been closed to give an obstructed appearance. The needle is kept well beneath the mucosa and in the superficial muscle to avoid the formation of thin blebs or blisters, which may rupture and cause loss of the paste.

Post-operatively, patients are asked to take warm sitz baths once or twice daily and are discharged with a 12 or 14 F Foley catheter, allowing oedema produced by the injections to subside. On the second or third post-operative day the catheter is removed and a voiding trial is performed. If the patient is unable to void or empty his bladder, the catheter is reinserted for a few more days. A broad spectrum antibiotic is prescribed pre- and post-operatively for 1 week.

All patients treated with transurethral injections had been incontinent of urine for a minimum of 1 year after their prostatectomy. Some had failed to respond to other incontinence devices and procedures and were most unhappy with their state.

The results of the injections were graded as excellent (when patients were completely continent and used no protective pads or tissues), good (when

patients improved and required only minimal protection), and failed (when there was no improvement). Improvement was defined as either an excellent or good result.

Results

Slightly more than 1000 injections were performed on the 720 patients (average 1.4 injections per patient and 18 ml Polytef paste per injection). Patients receiving Polytef injections because of post-TURP incontinence had an 88% improvement in their symptoms. In this group, 62% required only 1 injection. The open prostatectomy group of incontinent patients showed a 74.4% improvement and in the radical prostatectomy group 66.6% reported significant improvement (Table).

Table Results in 720 patients

	No. of patients	(%)	
<i>Turp</i> (n = 400)			
Cured	312	(78)	} 88
Improved	40	(10)	
Failed	48	12	
24 of 48 received only 1 injection			
<i>Open prostatectomy</i> (n = 172)			
Cured	96	(55.8)	} 74.4%
Improved	32	(18.6)	
Failed	44	(25.6)	
18 of 44 received only 1 injection			
<i>Radical</i> (n = 148)			
Cured	64	(43.3)	} 66.6%
Improved	36	(23.3)	
Failed	48	(32.4)	
16 of 48 received only 1 injection			

Post-operative complications were minimal and consisted primarily of a few days of urethritis and dysuria. There were 3 perineal abscesses, all of which occurred in our early experience when injections were being performed transperineally. A few patients experienced prolonged (2-3 weeks) perineal pain but responded well to anti-inflammatory drugs. It was not unusual to see elevated temperature on the first or second day following injections, even though both urine and blood cultures were found to be sterile.

In the improvement groups, 40% required 2 or even 3 injections; 69% of patients in the failure groups had only 1 injection. Other reasons for failure included a fibrotic urethra, post-operative leak of the paste, small bladder capacity and detrusor instability.

Discussion

We have identified 3 patterns of response to injections in the improvement groups. The first group improved immediately and remained dry. The second group resolved their incontinence slowly over a period of 3 to 7 months. The third group was dry immediately post-operatively but began to leak 1 to 3 weeks later. These patients became dry in approximately 3 to 7 months. We therefore wait at least 6 months before considering reinjection. These patterns of response need to be explained to the patient pre-operatively. Although most of our patients improved with only 1 injection, we recommend 2 or even 3 injections to achieve improvement if failure occurs after 1 injection. Polytef paste is a safe substance which has been used for many years in other areas of medicine (Arnold, 1962). We have not found particle migration, as suggested by Malizia *et al.* (1984), to be a clinically significant problem, and malignancy related to Teflon has not been reported.

In view of the ease of application and minimal side effects reported in this study, we recommend periurethral and transurethral injections of Polytef paste for the treatment of urinary incontinence. Polytef paste appears to be the most effective injectable substance available, giving the most consistent results with minimal complications.

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Is Injected Polytetrafluoroethylene (Polytef) Carcinogenic?

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Summary—Injectable polytetrafluoroethylene (Polytef) has been used in many patients for vocal cord augmentation and for the management of urinary incontinence since the early 1960s and non-injectable forms have been used for sutures, hernia repair, replacement of the stapes, hip prostheses, cardiac valves and vascular grafts.

Since 1984, many children have been treated with subureteric Polytef injection for the management of vesicoureteric reflux. Its use in young patients has heightened the concern about particle migration and carcinogenesis, particularly in view of the fact that the substance may be in the patient for decades.

The available evidence does not confirm a significant carcinogenic effect in humans; rather it suggests that, if there is a risk, it is extremely low. However, human specimens, taken decades after the implantation of Polytef, and long-term, non-rodent animal experiments are needed to substantiate the probable safety of Polytef in children.

Polytetrafluoroethylene (PTFE) was first invented in 1938 (Dupont de Nemours, 1988). The carbon-fluorine bonds enable PTFE to be used for the storage of sulphuric acid, to protect the Statue of Liberty, and to act as a heat shield to craft re-entering earth's atmosphere from outer space (Becmeur *et al.*, 1990). This stability, together with a low coefficient of friction, make it a highly effective coating for non-stick frypans.

The pyrolysis used for the manufacture of the polymer produces toxic products (difluorophosphene, perfluoroisobutylene and hydrofluoric acid) which are again released when the finished product is heated above 350°C (Bischoff, 1972). Thus rodents housed in a room with heated PTFE die from haemorrhagic lung disease caused by these toxic products (Harris, 1951; Truffett, 1958). A similar toxic effect is also seen in human lungs (Harris, 1951; Williams *et al.*, 1974; Brubaker, 1977; Haugtomt and Haerem, 1989).

It has been suggested that the breakdown products that cause the pulmonary complications

are found in small amounts within the finished product and, when released in the tissues, are responsible for a carcinogenic effect on cells (Bischoff, 1972). This theory is supported by the finding of particle migration from solid synthetic implants to regional lymph nodes (Tabatowski *et al.*, 1990), indicating that polymers can be broken down in the body, but it is refuted by more extensive experiments where malignancies were produced in rats with solid metal and polymer implants (Oppenheimer *et al.*, 1953, 1955, 1956) and less frequently with perforated polymers and virtually never with polymer powders (Oppenheimer *et al.*, 1961). Consequently, Oppenheimer's group suggested that mechanical irritation rather than a toxic product is the carcinogenic factor. The malignancies were found to develop in the capsule around the implants, even after the materials had been removed prior to the malignant transformation (Oppenheimer *et al.*, 1958).

Thousands of patients have had PTFE implants and in only 3 cases have there been reports of a malignancy adjacent to a PTFE implant (Lewy, 1966; Montgomery, 1982; Hakky *et al.*, 1989).

Most patients receive their PTFE implants late in life and several reports have shown the progression of histological change in these patients (Lewy, 1966; Boedts *et al.*, 1967; Harris and Hawk, 1969; Stone *et al.*, 1970; Goff, 1973; Rubin, 1975; Stephens *et al.*, 1976; Sanfilippo *et al.*, 1980), but there have been few studies of the tissue reaction after a significant number of years (Dedo and Carlöö, 1982; Wenig *et al.*, 1990). Arnold and Stephens (1980) found no malignancy in patients with up to 10 years' follow-up after vocal cord injection; Politano (1990) has not recorded malignancy in 15,000 patients treated for incontinence with Polytef injections since 1964 and there are no other reports of malignancy following the use of the solid forms of PTFE in humans.

Malignant transformation or cellular atypia may have occurred without any clinical manifestation in the many patients who have not been examined histologically. Although the human data thus far would therefore suggest that the risk is low, there is not sufficient published material to be certain of this.

The other major concern about the use of Polytef is the risk of migration. This does occur after both small (Boedts *et al.*, 1967; Malizia *et al.*, 1984; Aaronson, 1991) and large dose injections (Mittleman and Marraccini, 1983; Malizia *et al.*, 1987; Claes *et al.*, 1989). Polymer particle migration also occurs from solid materials such as heart valves (Weingarten and Kauffman, 1977), dialysis blood pump tubing (Leong *et al.*, 1982) and solid implants (Tabatowski *et al.*, 1990). The question is not "Does PTFE migrate?", but "Does the disseminated material have any adverse effect?", and the effect

that is of most concern is whether or not malignant transformation is stimulated in the long term.

Polytetrafluoroethylene in Humans

Two areas of study have indicated the effect of PTFE and its breakdown products in humans: the industrial medicine recognition of polymer fume fever, and the study of post mortem or biopsy specimens.

As for animal experiments on the pyrolysis products of PTFE, an extensive literature exists on the toxic effects on factory workers and others who have been exposed to the fumes of heated PTFE. Workers who either smoke contaminated cigarettes or inhale the toxic products while grinding or heating PTFE can develop fever, rigors, pulmonary oedema, pulmonary fibrosis or pericarditis (Harris, 1951; Williams *et al.*, 1974; Brubaker, 1977; Haugtomt and Haerem, 1989). Death has been recorded in one case (Becmeur *et al.*, 1990). The incidence of workers being affected has decreased since safety in industry has improved.

The Table lists the histological studies where the site of Polytef implantation has been examined, either as a post mortem specimen or from an excision biopsy. Patients whose vocal cords have been treated and urological patients (adults and children) are represented, including 2 lung specimens.

Progression of the histological changes appears similar to that seen in vocal cord injection in dogs (Kirschner *et al.*, 1966; Toomey and Brown, 1967). Initially there is an active inflammatory reaction with subsequent invasion by multinucleated giant

Table Histological Follow-up of Patients treated by Polytef Injections

<i>Authors</i>	<i>Site of injection</i>	<i>Implant to biopsy delay</i>	<i>No. of patients</i>
Boedts <i>et al.</i> (1967)	Vocal cords	4 weeks	1
Wilson and Gartner (1987)	Vocal cords	4 months	1
Marcellin <i>et al.</i> (1990)	Bladder	6 months	3
Stone and Arnold (1967)	Vocal cords	4–13 months	2
Lewy (1966)	Vocal cords	14 months	1
Stone <i>et al.</i> (1970)	Vocal cords	3–16 months	3
Goff (1973)	Vocal cords	4 days–18 months	2
Stephens <i>et al.</i> (1976)	Vocal cords	11–21 months	2
Claes <i>et al.</i> (1989)	Lung	24 months	1
Mittleman and Marraccini (1983)	Lung/urethra	24 months	1
Harris and Hawk (1969)	Vocal cords	25 months	1
Sanfilippo <i>et al.</i> (1980)	Vocal cords	34 months	1
Wenig <i>et al.</i> (1990)	Vocal cords	1 month–15 years	8
Dedo and Carlöö (1982)	Vocal cords	4 weeks–16 years	12

cells which engulf the Polytef particles and sequester them in vacuoles (Lewy, 1966; Boedts *et al.*, 1967; Stone and Arnold, 1967; Harris and Hawk, 1969; Stone *et al.*, 1970; Goff, 1973; Stephens *et al.*, 1976; Sanfilippo *et al.*, 1980; Dedo and Carlöö, 1982; Mittleman and Marraccini, 1983; Wilson and Gartner, 1987; Claes *et al.*, 1989; Marcellin *et al.*, 1990; Wenig *et al.*, 1990). Most of the late follow-up patients show a well circumscribed collection with a significant amount of incorporated collagen, without cellular atypia (Dedo and Carlöö, 1982; Wenig *et al.*, 1990). There have, however, been reports of late apparent enlargement of the PTFE-oma: 1 patient developed urinary obstruction (Boykin *et al.*, 1989), 1 an enlarged vaginal granuloma (Ferro *et al.*, 1988), and 3 reports have documented the development of a neck swelling many months after Polytef injection into paralysed vocal cords (Sanfilippo *et al.*, 1980; Wilson and Gartner, 1987; Wenig *et al.*, 1990). No malignant change was found in any of these patients and no other reports of significant enlargement of the implants have been published.

Three patients have been found to have a malignancy adjacent to a PTFE implant: (1) a single case of a fibrosarcoma adjacent to a PTFE aortic graft implanted 10 years earlier (Montgomery, 1982); (2) a patient with a chondrosarcoma of the vocal cord who had had a Polytef implant 6 years earlier (Hakky *et al.*, 1989); (3) a patient in Lewy's review series (1139 patients) had a carcinoma adjacent to the Polytef (Lewy, 1976). None of these tumours had a definite cause and effect relationship with the PTFE.

Arnold and Stephens (1980) did not record any instance of malignancy in the 100 patients treated for vocal cord paralysis with up to 10 years' follow-up and Politano (1990) found no malignancy in the 15,000 patients treated for urinary incontinence with Polytef since 1964. Unfortunately, neither of these centres has carried out systemic dissections of those patients who died many years after their injections of Polytef, and an unknown number of these patients may have had undetected subclinical secondary malignancy. The longest follow-up of the human histological response to Polytef is 16 years (Dedo and Carlöö, 1982).

Polytetrafluoroethylene in Animal Experiments

Animal experiments with PTFE and its pyrolysis products have fallen into 3 different groups: (a) rodents and larger animals (Harris, 1951; Truffett, 1958) have been exposed to the heated polymer in

confined spaces; (b) the short-term histological reaction to Polytef injections has been studied in rabbits (Arnold, 1962), dogs (Kirschner *et al.*, 1966; Toomey and Brown, 1967) and monkeys (Malizia *et al.*, 1984); (c) rodents have had solid, perforated and powdered forms of PTFE implanted as part of more extensive studies on the chemical versus mechanical carcinogenic effect of a wide range of metals and polymers.

Rats confined to a room with heated, solid PTFE (Harris, 1951), or heated PTFE-coated frypans (Truffett, 1958), developed haemorrhagic lung disease, and coagulative necrosis and lymphocyte infiltration of their liver and kidneys (Evans, 1973).

Arnold (1963), who initially developed the use of PTFE and glycerin mixture for vocal cord augmentation, studied the histological response in the rabbit quadriceps before injecting the material into human vocal cords. He examined the rabbit muscle 2 and 4 months after injection. Kirschner *et al.* (1966) and Toomey and Brown (1967) studied the local response in dog vocal cords after Polytef injection, and Malizia *et al.* (1984) demonstrated the local and distant reaction to injected and the subsequently migrated Polytef particles. They found no inflammatory reaction in the brain; otherwise, each of these animal studies showed a similar response to the injected material: after 2 weeks, islands of PTFE were surrounded by histiocytes and foreign body giant cells, with moderate numbers of lymphocytes and plasma cells. The central areas showed marked acute inflammatory changes with lakes of eosinophilic hyaline material and infiltrates of polymorphonuclear leukocytes. A similar reaction was seen at 2 and 3 months, with the acute inflammatory changes eventually being replaced with increasing numbers of foreign body multinucleate giant cells which contained phagocytosed PTFE particles within vacuoles, and there was an increase in the fibroblastic response with time. The longest follow-up in these studies was 18 months (Kirschner *et al.*, 1966). No malignant changes were seen in these animals and the evolution of change was similar to that seen in humans.

The third category of animal experiments has involved the implantation of solid, perforated and powdered forms of PTFE. The work by the team from the Institute of Cancer Research, Columbia University, New York, found that the mechanical effect of the implant caused the malignant transformation, not toxic chemicals in the implant (Oppenheimer *et al.*, 1953, 1955, 1958, 1961). They produced tumours with solid implants in 8 of 34

rats, with perforated materials in 6 of 32, with the powdered form in only 1 of 387. Other workers have demonstrated malignant transformation in the presence of subcutaneous PTFE implants (Tomatis and Parmi, 1971) and other synthetic polymers (Maekawa *et al.*, 1984), but not all investigators have been able to produce the same result. In studies by Bischoff and Bryson (1969) no sarcomas developed over 19 months in a group of 40 rats. The differences between these results and the results of the New York group may be explained by species, methodology or product variations.

Oppenheimer *et al.* (1958) found that the tumourigenic effect had a significant latent period and that tumours developed after the removal of the solid implanted polymer disc as long as it had been left *in situ* for at least 6 months. If the capsule around the implant was removed at the time of removing the foreign body, no malignancy developed.

It should be noted that rats are known to be prone to sarcoma development, which may mean the above results are unnecessarily alarming, but all of these studies were conducted over 2 years or less (the life-span of a rat), which may make a non-malignant result an invalid conclusion.

Discussion

The early experiments with rodents strongly suggested that the solid form of polymers, including PTFE, was associated with a high risk of malignancy, but when powdered forms were used virtually no sarcomas were formed after subcutaneous implantation. These findings refuted claims that toxic products within the polymers caused the malignant transformation, although these toxic pyrolysis products are the known cause of inhalation injury in humans and animals.

Short-term human and animal experiments suggest a gradual quiescence of the inflammatory response to Polytef paste, with incorporation of the Polytef particles into multinucleate giant cell vacuoles. There have, however, been 3 reported human cases of malignancy adjacent to PTFE implants. The evidence for PTFE as the causative agent is not strong, but equally important is the lack of a large number of long-term follow-up studies of patients to examine the Polytef injection sites histologically. Nevertheless, many thousands of patients have had long-term PTFE implants without the development of secondary malignant disease of clinical importance.

It appears that Polytef injection is not associated

with a significant risk of secondary malignancy, but large animal studies over a number of years and histological follow-up of patients who were injected many years ago should be conducted either to confirm or deny what is regarded by many as a safe procedure for the treatment of vesicoureteric reflux in childhood.

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Stamey-Martius Procedure for Severe Genuine Stress Incontinence

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Summary—There are few options now available to treat patients with severe genuine stress incontinence caused by urethral failure. These patients usually have a low maximum urethral closure pressure (< 20 cm of water) and anterior vaginal wall scarring caused by previous surgery. In 32 such patients we used the Martius fat pad insertion procedure, in addition to the Stamey procedure, and achieved a 91% symptomatic success rate over a mean 13-month follow-up period. Because of its simplicity, reliability and low morbidity, we recommend this procedure in this difficult group of patients before performing a sling procedure or insertion of an artificial urinary sphincter.

Successful surgery for genuine stress incontinence probably depends on the repositioning of the bladder neck and proximal urethra, and intrinsic urethral function. Endoscopic bladder neck suspension procedures (Stamey, 1973; Raz, 1981; Gittes and Loughlin, 1987; Parra and Shaker, 1990) are increasingly used to treat genuine stress incontinence with short-term and long-term success rates ranging from 96% (Boyd and Raz, 1984) to 57% (Spencer *et al.*, 1987). There is evidence (McGuire *et al.*, 1986; Sand *et al.*, 1987; Hilton and Mayne, 1989; Bergman *et al.*, 1989) to show that females with poor urethral function, as demonstrated by gross leakage on video-urodynamic studies and low maximum urethral closure pressure (< 20 cm H₂O), have a failure rate exceeding 50% after stress incontinence surgery. Such patients have usually had previous surgery and consequently, to a greater or lesser extent, have scarring of the anterior vaginal wall. We have used the Stamey procedure in conjunction with insertion of a Martius fat pad to treat these females with severe recurrent stress incontinence (Grade III).

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Patients and Methods

This study was conducted in 4 centres and 32 patients were included between June 1988 and February 1990; they were aged 16 to 88 years (mean 57). All had been investigated with urethral pressure profiles and video-urodynamics. They had undergone up to 6 previous operations (mean 1.9) (Table 1) and, in addition, 21 patients had had a previous hysterectomy. They had been incontinent for 1 to 52 years (mean 12) and used up to 18 pads per day (mean 6). Only 2 patients had demonstrable detrusor instability before undergoing surgery.

Table 1 Previous Operations for Stress Incontinence

Operation	No. of patients
Stamey	12
M.M.K.	6
Burch colposuspension	3
Sling	3
Manchester repair	2
Zacharin	2
Teflon injection	3
Urethrocleisis	1
Anterior vaginal repair	23
	(28 operations)

At operation a vertical incision was made in the labia majora (Fig. 1A) and the distinct fat pad within it (Martius, 1928) was dissected from above downwards, starting at the level of the pubic tubercle but carefully preserving its blood supply, which comes from the posterolateral aspect. An inverted U-shaped incision was made in the anterior vaginal wall with its apex in the mid-urethra (Fig. 1B) and the vaginal flap was dissected carefully from the proximal urethra and bladder base. A paravaginal tunnel was developed under the labia minora with blunt dissection and the pedicled fat graft was brought into the vaginal wound. The Stamey procedure was then performed, using 1-cm lengths of Silastic tubing and no. 2 nylon sutures (Abrams and Yande, 1988). The Martius fat was then fixed in the wound with catgut sutures (Fig. 1C). It is to be noted that the fat was made to lie outside the Silastic tubings used for the Stamey procedure. The vaginal wound was closed and the nylon sutures were tied sufficiently to stop the "incontinent jet" produced after filling the bladder. A suprapubic catheter was used until the patient was voiding satisfactorily (Fig. 1D). The average hospital stay was 4 days.

Post-operative urethral pressure profiles and video-urodynamic studies were repeated after 4 to 24 months (mean 13), with repeat assessment of symptoms.

Results

The symptomatic success rate was encouraging (Table 2). The urodynamic result was less impressive, but complete failure occurred in only 3 patients (9%). The number of pads used in the post-operative period decreased considerably (Table 3). There was no evidence of urethral compression with this procedure, as there were no statistically significant (paired *t* test-*P* values) differences in the pre- and

Table 2 Success Rate after Stamey-Martius Procedure

Success	No. of patients	(%)
<i>Symptomatic</i>		
Completely dry	23	(72)
Occasional leak only	6	(19)
No change	3	(9)
<i>Urodynamic</i>		
Completely dry	16	(50)
GSI at capacity only	11	(34)
GSI at volumes > 200 ml	2	(6)
No change	3	(9)

GSI = genuine stress incontinence.

Table 3 Comparison of Pre- and Post-operative Urodynamic Values

Parameter	Before operation (range)	After operation (range)	<i>P</i>
Pad usage (no./day)	6 (0-18)	1 (0-8)	<0.001
Maximum urethral closure pressure (cm H ₂ O)	19 (5-48)	24 (8-48)	0.092
Functional urethral length (cm)	2.1 (1.1-3.2)	2.4 (1.2-3.5)	0.069
Peak flow rate (ml/s)	25 (6-50)	27 (8-54)	0.853

post-operative values of maximum urethral closure pressure, functional urethral length and peak flow rate (Table 3). Only 2 patients had detrusor instability in the post-operative period.

The major post-operative complication was the formation of vaginal granulations (5 patients) but these disappeared after the application of silver nitrate sticks. One patient had to have her right-sided nylon suture removed because of groin pain. Voiding difficulty occurred in 2 patients; 1 had had a previous ileocystoplasty and the other had to perform intermittent self-catheterisation for 2 weeks only.

Discussion

Few options are available to treat patients with severe genuine stress incontinence after failed conventional surgery. These include sling procedures and the insertion of an artificial urinary sphincter. Sling procedures produce urethral compression leading to voiding difficulties and the insertion of an artificial sphincter is expensive and has other associated problems (Mundy, 1991).

The causes of failed conventional surgery have been summarised by Stanton (1985):

- (1) Failure to elevate the bladder neck.
- (2) Failure to approximate and align the urethra to the posterosuperior aspect of the symphysis pubis.
- (3) Lack of support to the posterior aspect of the proximal urethra and bladder.
- (4) Creation of a rigid, function-less urethra as a result of post-operative fibrosis (the frozen urethra).

The beneficial effects of the Stamey-Martius procedure are probably due to the Martius fat pad insertion procedure being added to a standard Stamey procedure. Elevation of the bladder neck is achieved by the Stamey procedure, which also helps in the alignment and approximation of the urethra to the posterior aspect of the symphysis pubis.

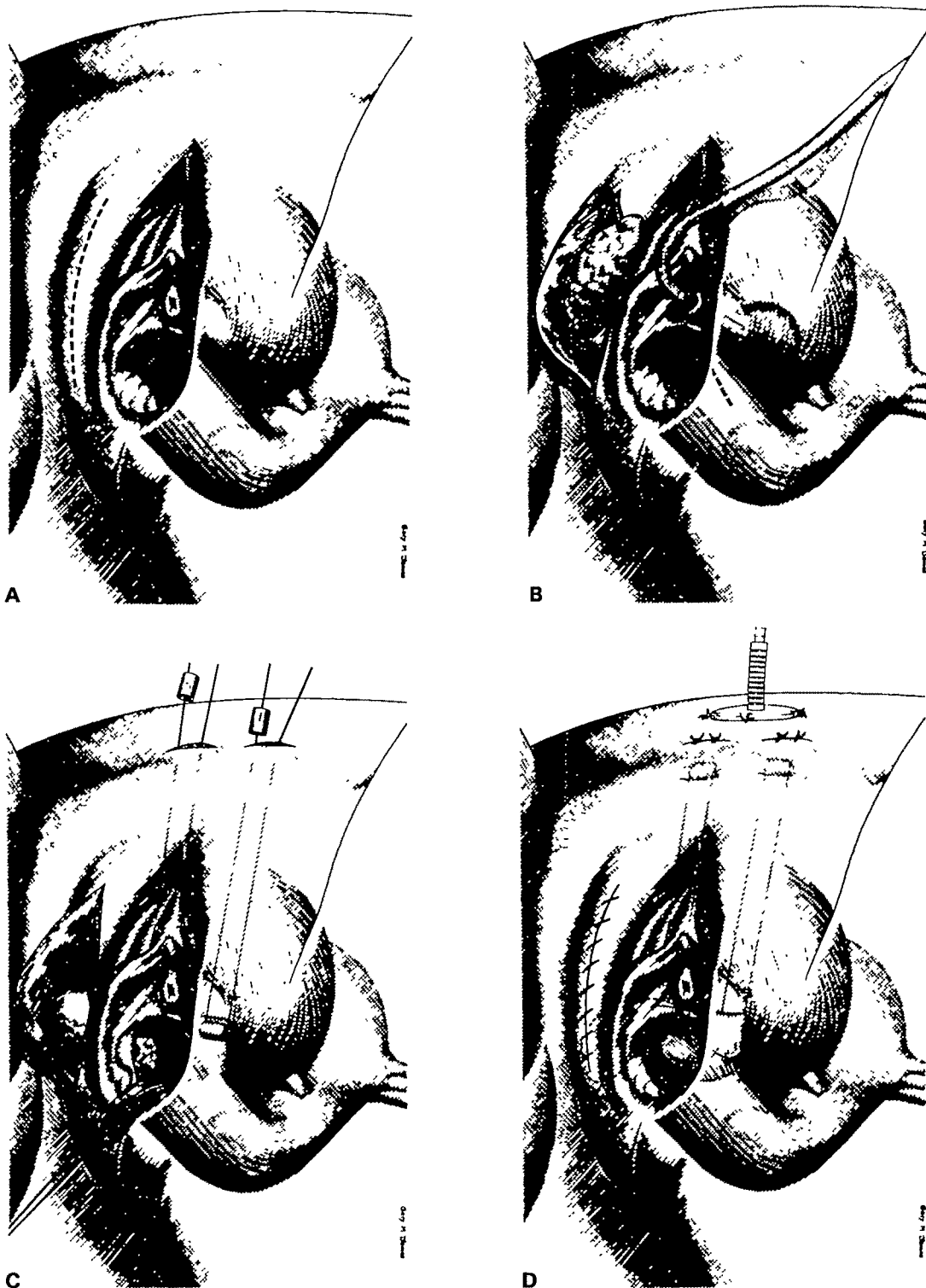


Fig. 1 (A) Vertical incision in labia majora to dissect the Martius fat. (B) Inverted U-shaped incision in anterior vaginal wall with its apex in the mid-urethra for dissection of vaginal flap. (C) After performing the Starkey procedure, the Martius fat was fixed in the vaginal wound. (D) Suprapubic catheter inserted at the end of operation, after tying the nylon loops and closure of wounds

Insertion of the Martius fat pad provides a buttress of well vascularised adipose tissue which supports the posterior aspect of the proximal urethra and bladder base. In addition, the fat pad also prevents adhesions forming between this area and the anterior vaginal wall, thus allowing the vaginal wall to move up and down freely during stress, without pulling the bladder neck open.

The Stamey-Martius procedure is simple to perform once the technique of Martius graft mobilisation has been learnt. Martius fat has been used widely in the repair of urethrovaginal and low vesicovaginal fistulae (Martius, 1928; Patil *et al.*, 1980). The procedure has a low morbidity rate, does not produce urethral compression, voiding difficulty or detrusor instability, and the hospital stay is short. Martius fat insertion could be easily performed in association with the Raz or other endoscopic bladder neck suspension procedures, if necessary.

In conclusion, the Stamey-Martius procedure is recommended in cases of severe genuine stress incontinence when conventional surgery fails, when the maximum urethral closure pressure is less than 20 cm H₂O or when there is excessive scarring of the anterior vaginal wall from previous surgery.

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Neurogenic Bladder Dysfunction in Lumbar Intervertebral Disc Prolapse

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Summary—Lumbar disc prolapse with urinary dysfunction is an uncommon condition. The clinical, pathological and follow-up details of 30 patients are presented. Detrusor recovery is rare and most patients are left with an areflexic bladder.

Female patients with lumbar disc prolapse and an areflexic detrusor who strain to empty their bladders are likely to develop genuine stress incontinence. This may be managed by the early institution of intermittent self-catheterisation, which may reduce the need for incontinence surgery.

Lumbar intervertebral disc protrusion (PID) is a common cause of orthopaedic and neurosurgical admission. The most frequent sites of protrusion are at the posterolateral positions of L4/5 or L5/S1. Central disc prolapse accounts for 1 to 15% of all prolapsed discs (O'Connell, 1951; Jennett, 1956) and may result in sacral nerve root compression (Emmett and Love, 1971) and urinary dysfunction, the commonest symptom of which is urinary retention (Fanciullacci *et al.*, 1989). In practice the distinction is somewhat academic, since patients with a posterolateral disc prolapse may develop sacral nerve compression due to medial migration of a large disc prolapse, resulting in the clinical features of the cauda equina syndrome. The somatic effects of disc prolapse are relieved more rapidly by laminectomy than the associated bladder dysfunction (Kostuik *et al.*, 1986).

The aim of this study was to assess our own experience and examine the indications for intermittent self-catheterisation (ISC) and incontinence surgery after PID.

Patients and Methods

A review of the records at the Spinal Injuries Unit, Lodge Moor Hospital, disclosed relevant data on

30 patients with lumbar disc prolapse and bladder dysfunction between 1970 and 1989. In all patients the diagnosis of a central disc prolapse was confirmed by myelography and all subsequently underwent laminectomy and removal of the extruded disc. The case records were surveyed and information was abstracted regarding the pre-operative clinical findings, surgery, post-operative urodynamics and clinical outcome. There were 16 men and 14 women (age range 24–68 years, mean 43). The time of referral after laminectomy ranged from 10 days to 5 years. All patients have been followed up for a minimum of 1 year (median 7 years, range 1–20).

Results

In 23 patients there was a long history of low back pain preceding their laminectomy. The commonest site of disc prolapse was L4/5 (Fig. 1); 26 patients, with severe back pain and neurological signs in their legs, developed urinary symptoms pre-operatively; 16 required catheterisation for urinary retention; 4 patients had no urinary symptoms prior to operation. The median duration of urinary symptoms prior to laminectomy was 24 h (range 12 h–10 days).

The method of bladder management at the time of referral to the Spinal Injuries Unit is detailed in Figure 2. Medium fill videocystometry was performed on 17 patients with persistent urinary

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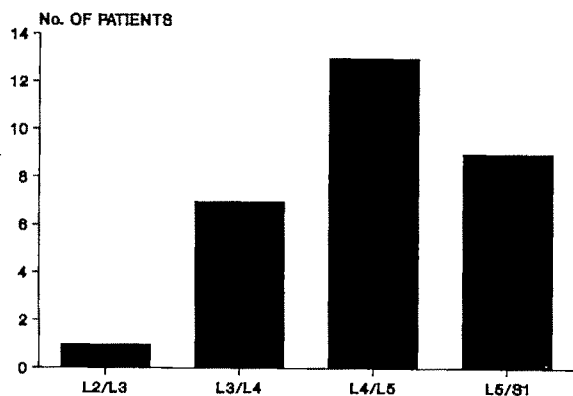


Fig. 1 Level of disc prolapse.

symptoms and incontinence. On cystometry, 11 patients had areflexic bladders and voided by straining. Four patients had detrusor hyper-reflexia associated with urinary incontinence and 2 had low compliance with opening of the bladder neck during filling. At bladder volumes in excess of 300 ml, 11 patients (7 female, 4 male) had genuine stress incontinence.

The early and late management of the patients is shown in Figure 2. Only 1 regained completely normal bladder function during the follow-up period. In the largest group, those with areflexic bladders, straining to void urine resulted in the development of stress leakage at large bladder volumes and 7 of these patients subsequently commenced ISC. With increasing experience more patients commenced ISC at the time of referral. Four patients required surgery for refractory incontinence and currently perform ISC; 2 patients had a colposuspension for genuine stress incontinence; 2 patients with detrusor hyper-reflexia producing

incontinence had a clam cystoplasty and are now dry.

No patient developed upper tract deterioration during the period of follow-up.

Discussion

Involvement of the cauda equina resulting in bladder dysfunction is a relatively uncommon though serious complication of lumbar disc prolapse. Clinical features of the cauda equina syndrome include disturbed micturition, retention of urine, loss of urethral sensation as well as constipation and impotence (Kostuik *et al.*, 1986). Sensory and motor changes in the sacral dermatomes also occur and the symptoms may be unilateral and asymmetrical. Urinary dysfunction may be a temporary feature of some patients with posterolateral disc prolapse and sciatica which may be due to pain and immobility. However, patients with the cauda equina syndrome usually have some sensory disturbance in the sacral dermatomes, although Emmett and Love (1967) reported 2 cases of urinary retention in women with no other neurological deficit.

Only 1 patient in this series regained normal detrusor activity; this may reflect a bias in the referral pattern. However, in patients who have had urodynamic investigation, detrusor recovery after central disc prolapse is uncommon and most patients are left with an areflexic detrusor (Anderson and Bradley, 1976; Fanciullacci *et al.*, 1989). Somatic function frequently improves after laminectomy, suggesting that visceral fibres are more vulnerable to the effects of disc prolapse. Surgery may also result in damage to the sacral nerve roots; 4 patients in this series had no urinary symptoms prior to laminectomy.

Shepherd (1959) proposed that early diagnosis and surgical decompression are important to minimise neural damage and promote recovery. Others (Jennett, 1956; O'Laoire *et al.*, 1981; Kostuik *et al.*, 1986) found no correlation between the time to surgical decompression and return of bladder function, although little objective assessment was made of detrusor function. The return of normal bladder function after laminectomy is gradual and may continue to improve for up to 3 years post-operatively (Jennett, 1956).

Of those patients who underwent urodynamics, 65% had detrusor areflexia and voided by straining, a finding similar to that of other series (Hellstrom *et al.*, 1986; Fanciullacci *et al.*, 1989). Progressive opening of the bladder neck during filling cysto-

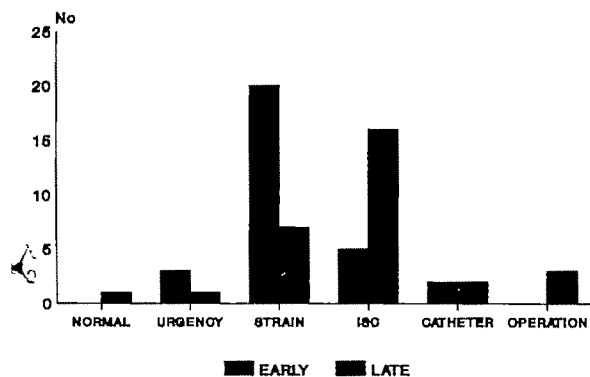


Fig. 2 Early and late management of patients with lumbar disc prolapse and bladder dysfunction.

metry is frequently seen in patients with PID. Repetitive straining may progressively damage the bladder neck, particularly in women, and result in stress incontinence, initially at high bladder volumes. In addition, many patients strain inefficiently and leave a large volume of residual urine, predisposing to urinary tract infection and urinary frequency. The early introduction of ISC obviates the need for straining and increases the functional bladder capacity. This may in turn decrease the indication for incontinence surgery.

Some patients have detrusor hyper-reflexia on medium fill cystometry, although the level of the disc prolapse is well below the conus medullaris. O'Connell (1951) suggested that the mechanism of injury for this hyper-reflexic group may be slowly progressive herniation of the disc irritating the nerve roots. However, the primary indication for surgery in the majority of our patients was the rapid development of urinary symptoms and signs. The effect of unopposed sympathetic activity on the human detrusor is unclear, although it is recognised that a functional obstruction of the distal sphincter may exist in patients with conus lesions (*i.e.* isolated distal sphincter obstruction) that is sympathetically mediated and can be abolished with alpha blockers (Clarke and Thomas, 1981). Symptoms of detrusor hyper-reflexia may coexist with sphincter weakness and, if refractory to anticholinergic therapy, can be managed with cystoplasty and colposuspension or artificial sphincter insertion.

The outlook for the return of detrusor function in patients with detrusor areflexia following lumbar disc prolapse is poor. Many patients can manage to empty their bladders by straining but later develop stress leakage at high bladder volumes. ISC provides a safe and reliable method of bladder emptying and may reduce the need for incontinence surgery.

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Intravesical Foreign Bodies: Five-year Review

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Summary—All manner of foreign bodies have been extracted from the bladder. Introduction into the bladder may be through self-insertion, iatrogenic means or migration from adjacent organs. Extraction should be tailored according to the nature of the foreign body and should minimise bladder and urethral trauma. Complete extraction should also be confirmed by panendoscopy at the end of the extraction procedure.

A 5-year review of our experience in this field has been conducted and the management and complications of intravesical foreign bodies are described. Of the 15 patients presenting to this department, 11 presented acutely and 4 presented with chronic symptoms due to complications which arose later. The possibility of an intravesical foreign body should be considered in any patient with chronic unexplained lower urinary tract symptoms.

Over the past few years there has been a noticeable increase in the incidence of patients presenting to casualty departments with foreign bodies lodged in body orifices. French *et al.* (1985) reported an increase with respect to rectal foreign bodies. The urinary bladder, however, would seem a more inaccessible site for the introduction of foreign bodies. It is therefore surprising that objects as diverse as light bulbs (Wenderoth and Jonas, 1980), plastic beans (Abdulla, 1990), blu-tack (Kelly and Young, 1988) and thermometers have been self-inserted by patients. Such objects are inserted usually for eroticism, inquisitiveness (particularly in children), as a consequence of disinhibited or disturbed behaviour (*e.g.* psychiatric or senile states) or under the influence of drugs, particularly alcohol. Some foreign bodies found in the bladder are iatrogenic in origin. Cases have been reported of suture materials and staples from bladder surgery (Edson and Kossov, 1980; Ward 1987) detaching and forming a nidus for stone formation. Objects such as severed or retained catheter tips from careless insertion/removal techniques have also been found (Karimi, 1978).

Intravesical foreign bodies provide a challenge to the urologist in both diagnosis and management.

Patients and Methods

Between 1985 and 1990, 21 patients with an age range of 19 to 91 years presented with intravesical foreign bodies to the urology departments in Bristol. Sixteen patients were male and 5 were female. Over the same period, 112 patients had been admitted for the removal of bladder stones (a ratio of foreign bodies to stones of approximately 1:5). Of the 21 patients, 15 presented acutely with symptoms directly attributable to the presence of the foreign body. These were primarily symptoms of bladder irritation and mucosal trauma. The 6 remaining patients presented at intervals ranging from 6 weeks to 6 years. Four of the patients presenting with acute symptoms had pre-operative X-rays prior to cystoscopy, while all of the patients presenting with chronic symptoms had their foreign bodies detected incidentally during routine lower urinary tract imaging. A broad classification of these foreign bodies falls into 3 different groups based on the method of their deposition in the bladder (Table 1).

Results

Of the patients who presented acutely, 3 were asymptomatic and presented of their own volition.

Table 1 Classification of Intravesical Foreign Bodies

A. Self-inserted:	sexual gratification paediatric psychiatric/senility drug intoxication
B. Iatrogenic:	bladder drainage bladder surgery adjacent surgery
C. Migratory.	uterus rectum vagina penetrating trauma

The remaining patients presented only after the development of symptoms. In many cases this delay occurred because the patients wished to avoid embarrassment and were too ashamed to admit self-insertion. These 13 patients presented with a combination of irritative bladder symptoms. Five had dysuria, 4 had haematuria, 4 had frequency, 2 had strangury and 3 had a urethral discharge. All objects from within the bladder were extracted in a one-stage endoscopic procedure using grasping forceps. Urethral dilatation was performed prior to removing 3 objects but a good case could be made for routinely dilating the urethra to minimise urethral trauma. The irrigating cystoscope was used successfully in every case bar one in which it proved unhelpful. This was a patient who had inserted a wax candle into her bladder which fragmented on attempted extraction. The individual wax fragments floating in the irrigant fluid were too difficult to grasp and the technique of air insufflation was used, during which the wax fragments fell to the bladder floor and were easily picked up with grasping forceps. The use of a lithotrite was required in 3 cases in order to break up large calculi that had formed around the foreign body. A thorough panendoscopy was performed at the end of every procedure to ensure the complete retrieval of all elements of the foreign bodies and to assess any concomitant urothelial trauma. There were no post-operative complications and all patients were discharged within 24 h.

The 6 patients presenting with chronic symptoms all had symptoms of recurrent urinary tract infection and had failed to respond to conventional antibiotic therapy prescribed by their family doctor. The foreign bodies were all diagnosed on initial KUB (kidney, ureter and bladder) examination after referral to the urology out-patient department. Intravenous urography did not contribute any further useful information. On reviewing the past medical history of these patients, the origin of the

foreign body was found in each case. One elderly patient, from whom a catheter tip was extracted, remembered having had a prostatectomy 5 years earlier following which he was told he had pulled his catheter out during an acute confusional episode in the night. He was recatheterised immediately and made a good recovery. In retrospect it is almost certain that the catheter fragmented on forceful removal and was not examined for completeness before insertion of a second catheter. He eventually presented with recurrent urinary tract infections and dysuria. An IVU revealed the catheter tip that was causing the symptoms (Fig. 1). Another elderly man had been in the habit of using a pipe cleaner to try to clear a urethral "blockage". On one occasion he pushed the pipe cleaner too far for retrieval and ignored its loss. On surgical removal of this foreign body it was noted that the pipe cleaner had curled up and acted as a nidus for a laminated bladder stone (Fig. 2).

A 65-year-old lady, who had undergone a Stamey procedure for stress incontinence 18 months previously, presented with symptoms of a bladder stone. At cystoscopy the stone was seen to be adherent to a nylon suture which had inadvertently been placed through the bladder wall.

A thorough gynaecological history taken from another patient revealed that 9 years previously a copper-"7" intrauterine contraceptive device (IUCD) had been "lost". A subsequent laparoscopy revealed the IUCD to be tightly wrapped in omentum. Attempts to retrieve this laparoscopically were unsuccessful and the patient declined the

**Fig. 1** Vermiform appearance of catheter tip in bladder.

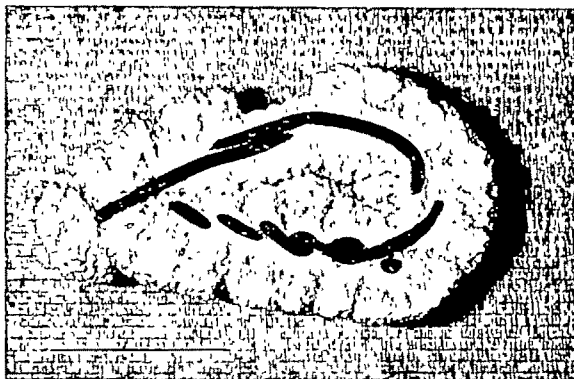


Fig. 2 Bladder stone formed on pipe cleaner.



Fig. 3 IUCD and bladder stone on plain film.

option of open surgical removal. At subsequent presentation with lower urinary tract irritative symptoms, a plain abdominal film (Fig. 3) revealed that the IUCD had migrated into the bladder, where it was seen to have been the nidus for a large stone.

The final case was that of a 72-year-old male who was found to have the retained tip of a suprapubic catheter. Six months previously he had been subjected to repeated attempts at suprapubic catheterisation when in acute urinary retention. The tip of the catheter must therefore have been sheared off by the trocar, which then lodged in the bladder mucosa. Again, full examination of the catheter used was clearly not performed; otherwise this

complication would have been discovered at the time.

Discussion

Intravesical foreign bodies are an important consideration in the differential diagnosis of lower urinary tract problems. Difficulty lies in patients who choose to ignore through embarrassment (or have forgotten) the insertion of the foreign body, or who do not consider it relevant to their present symptoms. One patient, obviously adept at instrumenting his urethra, was able to delay his presentation in urinary retention, secondary to a razor blade handle, by catheterising himself with a piece of rubber tubing around the foreign body.

Signs that should raise one's index of suspicion include undue patient anxiety during sexual questioning or attempts to avoid genital and rectal examination. Previous bladder procedures or surgery to adjacent organs may well be relevant when considering the possibility of the presence of a long-standing foreign body. Occasionally a disturbed patient will be ignored when he or she claims to have inserted a foreign body. Hickling and Lupton (1989) reported a psychotic patient who inserted a wrist-watch into her bladder and whose claims that she had done so were regarded by staff as delusional until she developed haematuria!

Investigation of a possible foreign body is usually simple. In the present series, all foreign bodies were detected on plain abdominal X-ray. Intravenous urography rarely contributed any additional information, although occasionally an unexpected radiolucent object may be detected. The marked preponderance of male patients in this series is probably due to their use of foreign bodies as a masturbatory aid, something that is rarely seen in females. For the object to reach the male bladder it must travel 20 to 25 cm, often also against the flow of urine. In several patients the object may have been accidentally pushed into the bladder while attempting to retrieve it. We uncovered a large variety of objects that were either inserted or migrated into the bladder (Tables 2 and 3).

A review of the world literature on this subject shows that almost every conceivable object has been inserted into the bladder and each one presents a fresh challenge in management to the urologist. The inquisitive nature of these patients makes it mandatory to ask directly about experimentation with intravenous drugs, *etc*, which may require their being managed as high risk cases. Objects from adjacent pelvic organs have occasionally been

Table 2 Foreign Bodies Presenting Acutely

<i>Object</i>	<i>Symptom</i>	<i>Mode of introduction</i>
Wax candle	Dysuria	Inebriated
Hair grip	Dysuria, haematuria	Eroticism with partner
Catheter tip	Strangury, haematuria	Patient cut catheter
Pipe cleaner	Haematuria, frequency	Attempted clearance of "blockage"
Safety pin × 2	Self-admission	Eroticism
Biro spring	Dysuria	"Curiosity"
Razor handle	Urethral discharge and haematuria	"Curiosity"
Matchstick	Dysuria and frequency	Eroticism
Drinking straw	Haematuria, dysuria	Erotic games
Cotton bud	Urethral discharge	"Self-hygiene"
Fountain pen cartridge	Frequency and blue urine	Attention seeking
ISC* catheter	Self-admission	Inserted too far into bladder
7.5 cm nail	Self-admission	Psychiatric disturbance
Piece of string	Urethral discharge, frequency	Psychiatric disturbance
Pen casing	Self-admission	Attempted

* Intermittent self-catheterisation

Table 3 Foreign Bodies with Delayed Presentation

<i>Object</i>	<i>Time interval</i>	<i>Mode of presentation</i>
Catheter tip	5 years	Recurrent UTI, lower abdominal pain
Pipe cleaner (calcified)	7 years	Recurrent UTI's, irritable bladder, bladder calculus on KUB
Calcified stitch after Stamey procedure	18 months	Recurrent UTI
Intrauterine contraceptive device	9 years	Recurrent UTI, chronic abdominal pain
Suprapubic catheter tip (sheared off by trochar)	6 months	Recurrent UTI

found to migrate into the bladder, *e.g.* thermometer from rectum (Kural *et al.*, 1987) and bone cement from hip arthroplasty (Wheeler *et al.*, 1983).

Management is aimed at providing complete extraction of the foreign body in as simple a technique as possible and with minimal trauma to the bladder and urethra. It is recommended that objects protruding partly into the urethra should be pushed fully into the bladder and examined cystoscopically prior to removal. The objects in the present series were all removed with cystoscopic grasping forceps but the literature abounds with ingenious modifications of conventional instruments that have been used to tackle difficult foreign bodies. Percutaneous instruments, with their straighter and stronger specifications, have been recommended (Walmsley, 1987; Schall *et al.*, 1989) for removal of large or irregular objects. Magnetic retrievers have been designed (Wise and King,

1989) to remove galvanic objects. The patient is protected from injudiciously forceful and potentially traumatic attempts at removal because the point of magnetic contact is lost if resistance is encountered. Chemicals retained in the bladder with a penile clamp in men have been used to dissolve some objects, *e.g.* xylol for wax foreign body dissolution (xylol is carcinogenic, however, and this practice is now not recommended). Although most objects may be removed transurethraly, open removal via suprapubic cystotomy or perineal urethrostomy is sometimes required for particularly large or awkward objects. Occasionally objects may be voided spontaneously even if their route of entrance was not transurethral, *e.g.* bullets lodged in the bladder (Abelsayed *et al.*, 1978). After removal, consideration should be given to the prevention of similar occurrences in future. The high percentage of chronic attenders and personal-

ity disorders seen in this subgroup of patients suggests that psychiatric referral should be considered at an early stage to prevent repeat presentations and the risks to which these patients expose themselves. These include bladder perforation, abscess and fistula formation. Chronic irritation and chronic sepsis caused by the presence of foreign bodies have also been described (Wyman and Kinder, 1988). The finding of 3 catheter tip foreign bodies in the present series, particularly in the current medico-legal climate, makes a case for routine examination of all catheters after removal. The finding of an incomplete catheter should prompt a further cystoscopy.

It is difficult to be certain that the incidence of foreign bodies in the bladder is on the increase, as is the case with the rectum, but the fact that an easily diagnosable and easily removable foreign body may be present in the bladder should be borne in mind, particularly in cases of chronic urinary tract infections refractory to medical treatment.

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Koilocytosis in Neoplasia of the Urinary Bladder

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Summary—Koilocytosis is commonly regarded as indicative of human papilloma virus infection in the uterine cervix. In 1987 morphologically similar changes were reported in bladder tumours. This is confirmed in the present study, the incidence here being 65%. In addition the incidence of koilocytic change was shown here to increase from non-infiltrative WHO grade I to infiltrative WHO II lesions, and to be more common in bladder lesions in women with cervical koilocytosis. The latter is in keeping with our previous report that the incidence of koilocytosis in the cervix of patients with bladder neoplasia is higher than expected in the general population, adding support to the hypothesis that both lesions may be virus-related.

The presence of epithelial cells with pyknotic nuclei and large perinuclear spaces, koilocytosis, is said to be indicative of human papilloma virus infection when it occurs in the uterine cervix (Fletcher, 1983). Similar changes have been reported in a small series of bladder tumours (Bryant *et al.*, 1987). In this district women with bladder neoplasia have a higher incidence of cervical koilocytosis than case-matched controls (Hartveit and Mæhle, 1989). This prompted us to investigate a series of cases with material from both bladder and cervix to see if koilocytosis was present in both. The bladder series was extended to see if the presence/absence of koilocytosis was affected by the histology of the tumour.

Patients and Methods

Between 1981 and 1986 inclusive, specimens were received from 160 women with bladder neoplasia. In 47 of them (the study group) we also had material (histological/cytological) from the uterine cervix. In all cases the date of birth was recorded. The bladder lesions were classified histologically as papillomas, non-infiltrative papillary carcinomas including carcinoma *in situ*, or infiltrative papillary

carcinoma. The carcinomas were further graded according to the classification recommended by WHO (Mostofi *et al.*, 1973). The bladder series was extended by the selection of a further 47 women from those with bladder neoplasia but without cervical specimens. Each patient was age-matched to the study group, and matched with regard to the histology of the bladder lesion. (Fig. 1).

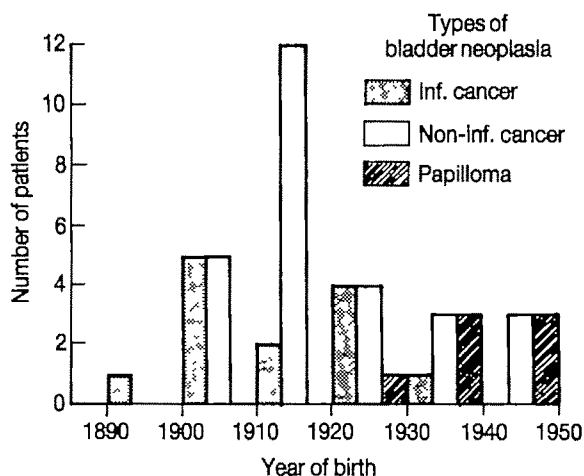


Fig. 1 The age distribution of women in the study group, related to the type of bladder neoplasia present

The histological material had been formalin fixed, paraffin embedded and stained with haematoxylin/eosin/saffron. The gynaecological cytological specimens had been "spray fixed" and stained by the Papanicolaou method. They had been examined for koilocytosis by the screening staff in connection with their routine duties. The criteria that had been used for the diagnosis of koilocytosis in the cervical material were those recommended by Coleman and Richman (1985), *i.e.* the presence of epithelial cells with pyknotic nuclei and large perinuclear spaces. Similar criteria were subsequently used when recording the changes in the bladder specimens.

Results

Koilocytosis (illustrated in Figure 2) was found in 61 of the 94 bladder lesions (65%). Its presence was not related to the age of the patients (Table 1). It was common in all types of lesions examined (Table 2), including papilloma. The incidence was lowest with non-infiltrative carcinoma WHO grade I (15 of 30) and highest with infiltrative carcinoma WHO grade II (9 of 10). The excess of positive grade II lesions (irrespective of infiltration) over grade I was statistically significant ($\chi^2=4.85$, $P<0.027$). The level was lower in grade III cases.

Koilocytosis was present in the cervical epithelium in 12 of the 47 women with bladder neoplasia. Three of them also showed cervical dysplasia (Table 3). In 6 of these 12 the bladder lesion also showed koilocytosis. (A further patient with cervical dysplasia without koilocytosis also showed koilocytosis in her bladder lesion). Comparison of the number of patients with/without koilocytosis in the bladder versus cervix (Table 4) shows that these 2 events occurred simultaneously more often than would be expected in a chance relationship ($\chi^2=4.02$, $P=0.04$).

Discussion

This study confirms that koilocytosis may occur in neoplastic transitional epithelium in addition to cervical squamous epithelium. The change was frequent in papillomas and carcinomas, but lower with infiltrating carcinomas WHO III. The latter probably reflects the difficulty in recording fine morphological changes in highly anaplastic lesions. Between these 2 extremes the level of koilocytic change rose from non-infiltrative to infiltrative lesions and with grade. This supports the thesis that this is a biological phenomenon rather than a

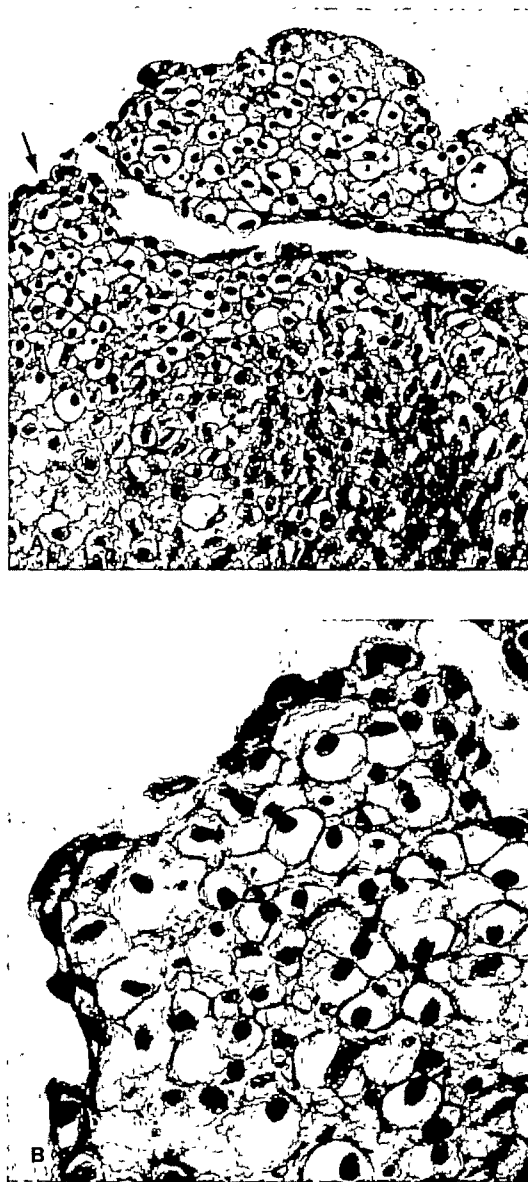


Fig. 2 Bladder papilloma with koilocytosis. Note the pyknotic nuclei in the transitional epithelial cells with perinuclear halos. The arrow on (A) marks the area enlarged on (B). Haematoxylin, eosin and saffron $\times 225$ (A) and $\times 560$ (B).

non-specific change. The overall frequency in this series was 65% compared with 82% reported previously (Bryant *et al.*, 1987). In view of the differences recorded here related to the histology of the lesion this could be due to differences in the composition of the material.

The series of 160 women with bladder neoplasia on which the present study is based showed a 17%

Table 1 Presence/Absence of Koilocytosis in Bladder Neoplasia Related to Age of Patient

Year of birth	Koilocytosis in bladder neoplasia		No. of patients
	+	-	
1890-	1	1	2
1900-	17	7	24
1910-	23	15	38
1920-	11	5	16
1930-	5	3	8
1940-	4	2	6
Total	61	33	94

Table 2 Presence/Absence of Koilocytosis in Bladder Lesions Related to Histology

Bladder lesion	Koilocytosis		No. of patients	(%+)
	+	-		
Papilloma	10	4	14	71
Non-inf. cancer				
WHO I	15	15	30	50
WHO II	17	7	24	71
Inf. cancer				
WHO II	9	1	10	90
WHO III	10	6	16	62
Total	61	33	94	65

Table 3 Presence/Absence of Koilocytosis in Neoplastic Bladder Lesions in 12 Women with Cervical Koilocytosis

Bladder lesion (WHO grade) in women with koilocytes in cervical specimen	Koilocytosis in bladder lesion		Total
	+	-	
Papilloma	1	2	3
Non-inf. carcinoma			
(I)	3*	2*	5
(II)	2	2*	4
Inf. carcinoma	0	0	0
Total	6	6	12

*Cervical dysplasia in addition.

Table 4 Comparison of Number of Patients with/without Koilocytosis in Bladder *versus* Cervical Lesions

Koilocytosis		Uterine cervix		Total
		+	-	
Bladder tumour	+	6	28	34
	-	6	7	13
Total		12	35	47

incidence of koilocytosis in the 41 gynaecological smears available and koilocytosis in 5 of 6 cervical biopsies plus 2 cervical polyps (Hartveit and Mähle, 1989). The incidence of koilocytosis in our non-neoplastic gynaecological cytology is less than 1%. The present work demonstrates that this excess of cervical koilocytosis is accompanied by a high level of koilocytosis in concomitant bladder lesions, suggesting that both may be of common viral aetiology. Too little histological material was available from our paired samples for valid comparison of viral activity in the 2 lesions. However, Bryant *et al.* (1987) found that papilloma virus common structural antigen was present in 7 of 50 neoplastic bladder lesions, and human papilloma virus antigens have been recorded in a urethral condyloma (Syrjänen and Pyrhonen, 1983). Thus the possibility of a common viral aetiology for these lesions cannot be dismissed.

The findings reported here may indeed represent the tip of an iceberg. Cervical lesions of viral aetiology are common in young women, while those with bladder lesions tend to be older. The other women in this series may thus have had a transient cervical infection at an earlier date.

Acknowledgement

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DNA Analysis in Predicting Survival of Irradiated Patients with Transitional Cell Carcinoma of Bladder

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Summary—A total of 115 patients with invasive transitional cell carcinoma of the bladder underwent radical radiotherapy between 1975 and 1986 and were followed up until the end of 1990. Apart from routine clinical observations, flow cytometric DNA measurements made on fresh tumour material were available for analysis. Actuarial cancer-free survival controlling for response to treatment was analysed with the log-rank test, bivariate and multivariate analyses using Cox's stepwise regression model on probable prognostic factors.

The overall actuarial 5-year cancer-free survival rate was 30%. Survival was significantly correlated with response to treatment: 59% for patients with complete regression and 5% for those with residual tumour.

Prognostic factors that significantly correlated with death from cancer were advanced stage, large size, incomplete resection, ureteric obstruction, anaemia, carcinoma *in situ* grade 3 and occurrence of more than one aneuploid cell population. However, only 3 of these factors were of independent power in the multivariate analysis: stage, size and carcinoma *in situ*.

Of 21 patients with a history of primary or secondary carcinoma *in situ*, 19 died from cancer during follow-up: 18 of the 21 patients had tumours that were aneuploid with more than one aneuploid cell population.

It is concluded that curative radiotherapy can be successful only in patients with less advanced tumours assessed according to clinical stage and size, aneuploid tumours with not more than one aneuploid cell line, no carcinoma *in situ*, no ureteric obstruction, and in whom a complete transurethral resection of the exophytic tumour is possible.

The best option when treating patients with transitional cell carcinoma of the bladder requiring radical therapy is still a matter for debate. Some favour radical cystectomy, with full-dose radiotherapy used only in patients not fit for major surgery (Whitmore *et al.*, 1977; Droller, 1985; Shipley *et al.*, 1985; Gospodarowicz *et al.*, 1989). Others advocate a policy of primary radiotherapy as definitive management and secondary cystectomy in all patients who fail to respond to therapy (Hope-Stone *et al.*, 1981; Quilty *et al.*, 1986; Jenkins *et al.*, 1988). Although the selection of patients for

radiotherapy in many series is largely negative, local tumour control and preservation of bladder function in about one-third of the patients can be expected (Greven *et al.*, 1990). If the radioresponsiveness of the tumour could be predicted more accurately before radiotherapy, presumptive non-responders could be offered alternative treatment and responders avoid the sacrifice of sexual and bladder functions that a cystectomy implies.

Accordingly, an extensive search has been made for prognostic factors before radiotherapy. Factors that have been shown to influence prognosis are depth of invasion, *i.e.* stage (Droller, 1986), ureteric obstruction, complete transurethral resection, pre-treatment haemoglobin level, configuration of the tumour (solid or papillary) (Shipley *et al.*, 1985),

squamous cell metaplasia (Martin *et al.*, 1989) and coexistent carcinoma *in situ* (Wolf *et al.*, 1985; Gospodarowicz *et al.*, 1989).

Flow cytometry has been available for over 15 years and its use in clinical practice is continually increasing. In the field of bladder cancer it has been widely documented both in diagnostics and therapy (Tribukait, 1984). The DNA value and the degree of proliferation can be correlated with tumour grade and depth of invasion, recurrence rate and survival (Gustafson *et al.*, 1982). Flow cytometry has also been used to identify specific tumour cases before therapy as well as monitoring patients during therapy (Bretton *et al.*, 1989).

Earlier studies from this institution have also shown that flow cytometry provides some basis on which the response to radiation, *i.e.* local control, can be predicted (Wijkström *et al.*, 1984; Wijkström and Tribukait, 1990). However, simply classifying tumours as diploid or various forms of aneuploid does not facilitate the separation of these tumours in the same way as it does among less advanced tumours. The aim of this study was to investigate the role of flow cytometry DNA analysis and other clinical prognostic factors in predicting survival in a series of patients with invasive, mostly grade 3, transitional cell bladder cancer treated with full-dose radiotherapy.

Patients and Methods

A total of 115 patients with invasive bladder cancer (86 men and 29 women, mean age 70 years, range 52–83) underwent radical radiotherapy (64 Gy for 7 weeks via a 6 MeV linear accelerator with 3-field technique) between 1975 and 1986 and they were followed up until the end of 1990.

The tumours were classified according to the tumour, nodes and metastases (UICC, 1978) and World Health Organisation (Mostofi *et al.*, 1973) systems (Table 1).

Response to therapy was assessed at follow-up cystoscopy performed 3 months after irradiation

therapy. Cystoscopy was performed with the patients under local anaesthesia together with bimanual palpation and cytological analysis of a bladder washing specimen. A biopsy was always performed if these investigations indicated residual tumour or recurrence. No form of imaging technique was used. Successive clinical follow-up was performed every 3 months for 2 years, every 6 months for up to 5 years and yearly thereafter.

Of the 115 patients, 32 were given various forms of chemotherapy at recurrence after completion of radiotherapy, but there was no obvious improvement. Six patients underwent a salvage cystectomy but all except 1 died in the post-operative period.

Survival was analysed according to response to radiation and various clinical prognostic factors recorded before radiotherapy. These factors included flow cytometric data (degree of ploidy and proportion of S-phase cells), grade, stage, carcinoma *in situ* before tumour progression, age, sex, early or late admission (before or after 1980), tumour configuration (solid or papillary), number of tumours, size, type of operation (biopsy or complete resection of the exophytic part of the tumour), presentation in time (primary or recurrent), haemoglobin level and intravenous urography.

Our methods of cell preparation, staining and standardisation of the flow cytometer (ICP 11) have been described in detail previously (Tribukait, 1987). After mechanical dispersion, fixation of cells in 96% ethanol, pepsine and RNase treatment, the suspension of single cell nuclei was stained with ethidium bromide. Human lymphocytes were used as external standard.

The results were presented as DNA histograms classified either as diploid or aneuploid with one or several cell lines. Two aneuploid cell lines were considered to exist if 2 distinct peaks were found in an aneuploid position in one histogram, or if aneuploid peaks with modal DNA values differing at least 0.4 c from each other were found in histograms from different samples on the same occasion. The proportion of S-phase cells was calculated after background subtraction.

Wherever possible, the DNA histograms from the tumour biopsies were used rather than those from bladder washings. There were 91 tumour biopsies and 108 bladder washing specimens available for pre-irradiation DNA analysis. Before 1980 it was more common that either biopsy or bladder washings were not available for DNA examination.

The endpoint of the analysis was relative survival (cancer-free survival). Survival was calculated after

Table 1 Pre-treatment Grade and Stage in 115 Patients who underwent Radical Radiotherapy

Grade	Stage					Total
	T1	T2	T3a	T3b	T4	
2	2	1	2	2	2	9
3	17	29	13	34	13	106
Total	19	30	15	36	15	115

the completion of radiotherapy (analysis started 3 months after the treatment was begun) until the last available follow-up date. In the calculation of cause-specific survival, patients dying of known unrelated causes without active bladder cancer present were excluded at death as not eligible for further follow-up. Survival curves were calculated using the Wilcoxon-Gehan method (Peto *et al.*, 1977) and the log rank test was used. Bivariate and multivariate analysis of probable prognostic factors for survival were performed with Cox's stepwise regression analysis (Kalbfleisch and Prentice, 1980). The stepwise procedure implies that the most significant factor is first taken into the equation in the first step. In the second step, the most significant factor of the remaining factors is taken into the equation, and so on. A *P* value below 0.05 was considered statistically significant.

Results

Overall survival and response to radiation

The overall actuarial relative (cancer-free) 5-year survival rate was 31%. Patient survival was significantly correlated with response to treatment at the first follow-up cystoscopy. Complete regression was associated with a significantly improved probability of long-term survival (59% at 5 years versus 5% for those who had residual tumours at 3 months) ($P < 0.001$) (Fig. 1). A total of 55 patients (48%) had no evidence of cancer and 60 patients (52%) had either local recurrence or incomplete regression at their initial examination 3 months after complet-

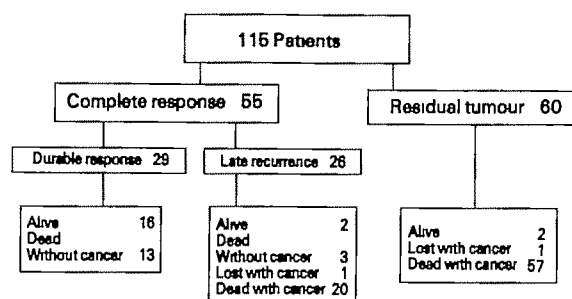


Fig. 2 Clinical course according to radiation response at first follow-up cystoscopy at 3 months

ing radiotherapy. At the end of the follow-up period (1990) 20 patients were alive, 2 had been lost to follow-up, 16 had died from other causes while free of cancer and 77 (20 with recurrent cancer) had died from cancer (Fig. 2).

Grade and stage

Only 9 patients had grade 2 tumours, the remaining 106 patients having grade 3 tumours. These numbers were too small to prove any statistically significant difference in survival.

Patient survival was, however, significantly correlated with T category ($P = 0.022$). The stages were separated into 2 categories— $\leq T3a$ and $\geq T3b$ (Fig. 3). For comparison, the mortality for the various stages is shown in Table 2. When stage and radiation response were analysed together the difference in survival was even more pronounced (Fig. 4).

Carcinoma in situ

Randomised biopsies of macroscopically unaffected bladder epithelium was not routinely performed in this series but in 21 patients carcinoma *in situ* (CIS) grade 3 had been diagnosed; 19 of these 21 patients died from bladder cancer (10 had distant metastases), 1 died from other causes while free of cancer after 16 months, and the remaining patient is alive after salvage cystectomy. Thus the 5-year cancer-free survival rate differed significantly between patients with (8%) and without (35%) a history of carcinoma *in situ* ($P = 0.050$).

Endoscopic findings and completeness of pre-treatment resection

There was no statistical difference in survival when separating tumours into papillary (26) and solid (87) or single (78) and multiple (35) tumours. However, small size (the tumours were separated into smaller (40) or larger (73) than 3 cm) was

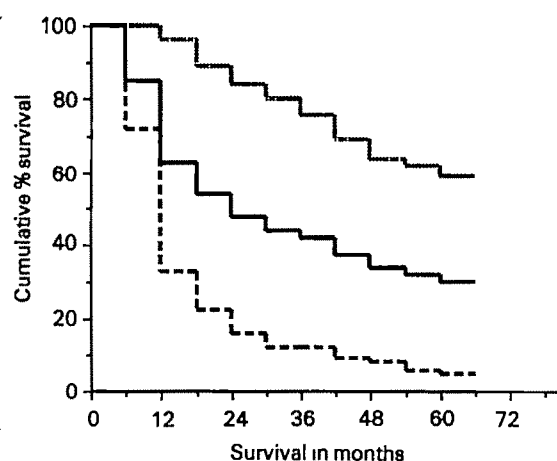


Fig. 1 Relative survival according to radiation response at first follow-up cystoscopy at 3 months. — All patients (115), 5-year survival rate 30%. - - - Complete regression (55), 5-year survival rate 59%. Incomplete regression (60), 5-year survival rate 5%. Log Rank test overall < 0.001 .

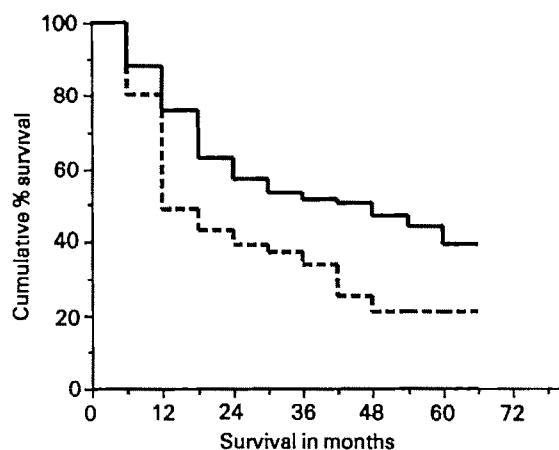


Fig. 3 Relative survival according to stage. — $\leq$ T3A (64), 5-year survival rate 39% — $\geq$ T3B (51), 5-year survival rate 21%. Log Rank test overall $P=0.022$.

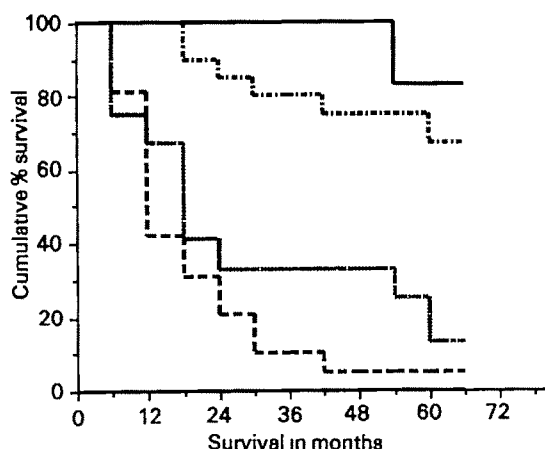


Fig. 4 Relative survival according to stage and radiation response at first follow-up cystoscopy at 3 months. — Complete response: $\leq$ T3A (29), 5-year survival rate 83% — Complete response: $\geq$ T3B (25), 5-year survival rate 67%. Incomplete response: $\leq$ T3A (35), 5-year survival rate 13%. — Incomplete response: $\geq$ T3B (26), 5-year survival rate 5%.

associated with a significantly improved survival at 5 years ($P=0.004$).

Complete resection of the exophytic part of the tumour was performed in 54 patients and the resection was incomplete in 61; 14 of these 61 patients (23%) had no clinical sign of tumour at the first follow-up compared with 36 of 54 patients (67%) with an apparently complete resection. Survival differed significantly at 5 years between these 2 groups ($P=0.003$) (Fig. 5).

Intravenous urography (IVU) and pre-treatment haemoglobin level

Obstruction seen on IVU (33 of 87 patients who had been examined shortly before radiation) implied a reduced 5-year survival rate (22%) compared with a normal outflow of urine (54 patients) (41%) ($P=0.003$). A haemoglobin level below 12 g/dl was also consistent with a poorer relative 5-year survival rate than a level over 12 g/dl (11 and 34% respectively) ($P=0.033$).

DNA flow cytometry

Tumours were separated into diploid and various forms of aneuploid tumours (diploid (7); triploid (47); tetraploid (5); $>$ tetraploid (10); aneuploid with more than one cell line (46)). Table 3 presents the observed mortality in cancer for the various degrees of ploidy. Actuarial cancer-free survival was, however, only calculated for 3 categories (2c (7); all aneuploid with one cell line (62); aneuploid with more than one cell line (46)). The presence of more than one aneuploid cell population was significantly associated with death from cancer at 5 years ($P=0.025$) (Fig. 6).

The presence of more than one aneuploid cell line was also strongly associated with the presence of carcinoma *in situ*. Of 21 patients with carcinoma *in situ*, 18 had more than one aneuploid cell line.

The proportion of S-phase cells expressing proliferation rate was generally high (median value 18%)

Table 2 Cancer Mortality in 115 Patients according to Stage during Follow-up 1975–1990

Status/stage	Alive or dead without cancer (%)	Dead, cancer (%)	Total
T1	8 (42)	11 (58)	19
T2	13* (43)	17 (57)	30
T3a	6 (40)	9 (60)	15
T3b	8 (22)	28 (78)	36
T4	3 (20)	12 (80)	15
Total	38	77	115

*Two lost alive with cancer

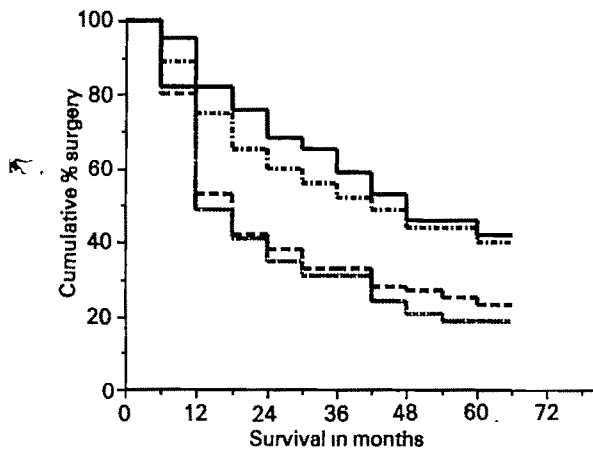


Fig. 5 Relative survival according to size and pre-treatment resection. — ≤ 3 cm (42), 5-year survival rate 42% — > 3 cm (73), 5-year survival rate 23%. - - - Complete resection (54), 5-year survival rate 40% Incomplete resection (61), 5-year survival rate 19%. Log Rank test overall $P=0.004$ and $P=0.003$ respectively.

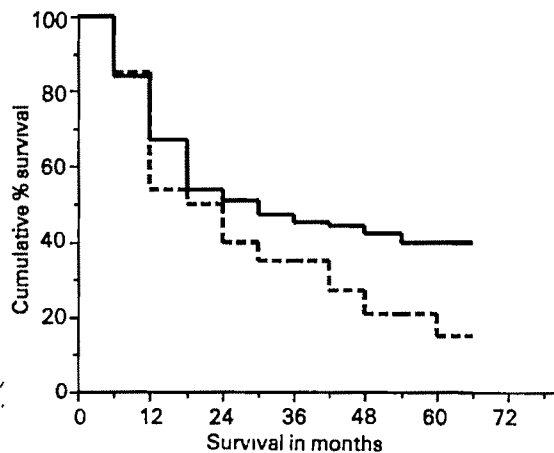


Fig. 6 Relative survival according to degree of ploidy in 108 patients (7 patients with diploid tumours have been omitted). — Aneuploid, one cell population (62), 5-year survival rate 40%. - - Aneuploid, $>one$ cell population (46), 5-year survival rate 15%. Log Rank test for trend $P=0.029$.

but was not significantly associated with survival at 5 years.

There was no difference in the ploidy pattern between the tumours that metastasised and those that did not.

Age, sex, admission and presentation in time

Age, sex, admission before or after 1980 and whether the tumour was primary or recurrent were not correlated with survival.

Bivariate and multivariate analysis on relative survival and response to radiation

In the bivariate analysis the prognostic factors were tested individually by the χ^2 test (Table 4). Significant factors from the bivariate analysis were competing factors of the multivariate analysis (radiation response, stage, size, extent of resection, IVU, Hb level, CIS and ploidy). Compared with individual testing of the variables the multivariate analysis selects variables with "independent" power. The logistic regression revealed 4 significant variables related to the relative cancer-free 5-year survival: radiation response, stage, carcinoma *in situ* and size. Table 5 shows the factors that simultaneously best explained the variation in the dependent variable.

Discussion

Complete local regression of the tumour after radiotherapy was found to be the most important predictor of cancer-free survival. Local response is, however, difficult to predict from clinical parameters hitherto used. Two of the most important factors are tumour size and depth of invasion, since each fraction of irradiation can only eradicate a certain proportion of the tumour cells. Therefore we also have to take into account the extent of the initial transurethral resection (Shipley *et al.*, 1987) before local tumour control can be related to the effect of irradiation. For example, in the present

Table 3 Mortality in 115 Patients according to Ploidy

Status Ploidy		Alive or dead without cancer (%)	Dead, cancer (%)	Total
Diploid		4 (57)	3 (43)	7
Aneuploid	Triploid	17* (36)	30 (64)	47
	Tetraploid	3 (60)	2 (40)	5
	$>$ Tetraploid	4 (40)	6 (60)	10
	$>one$ cell population	10 (22)	36 (78)	46
Total		38	77	

*Two lost to follow-up alive with cancer

Table 4 Cox Regression Analysis on Relative Survival (bivariate analysis). Prognostic Factors for Survival in 115 Patients with Invasive Bladder Cancer Subjected to External Radiotherapy. Dependent Variable Time to Death

Factor	Coding	β	χ^2	P	
Radiation response	0/1 0=yes/1=no	1.97	52.9	<<0.001	***
Grade	0/1 0=G3/1=G2	0.354	0.8	0.375	NS
Stage	0/1 0=T1-T3a/1=T3b-T4	0.378	5.3	0.021	*
Carcinoma <i>in situ</i>	0/1 0=no/1=yes	0.522	3.9	0.050	*
Solid/papillary	0/1 0=pap/1=sol	0.389	1.9	0.168	NS
No. of tumours	0/1 0=single/1= multiple	0.258	1.2	0.283	NS
Size	0/1 0= ≤ 3 cm/1 > 3 cm	0.754	8.3	0.004	**
Operation	0/1 0=resection/1=biopsy	0.686	8.8	0.003	**
IVU	0/1 0=normal/1=obstruction	0.831	9.2	0.003	**
Hb	0/1 0>12/1 $\leq$ 12	0.570	4.6	0.033	*
Ploidy	0/1/2 0=2 c/1=Aneupl./2=Aneupl. > one cell line	0.458	5.0	0.025	*
Proliferation	0/1 0= ≤ 18 /1=>18	0.069	0.1	0.795	NS
Age	0/1 0= ≤ 70 /1=>70	0.065	0.1	0.780	NS
Sex	0/1 0= male/1=female	0.083	0.1	0.750	NS
Admission	0/1 0=>1980/1= $\leq$ 1980	0.184	0.6	0.439	NS
Primary/recurrent	0/1 0=prim/1=rec.	0.348	1.9	0.170	NS

series only 23% of the patients who had incomplete resections were tumour-free at the first clinical follow-up compared with 67% of the patients who had an apparently complete resection.

Stage and size were also both of independent value for predicting cancer-free survival in this series. Depth of invasion is probably the best examined prognostic factor to date (Jewett and Strong, 1946), although stage is known to have pitfalls and can never be accurately elevated if there is no surgical confirmation (Schmidt and Weinstein, 1976).

In the present series, progressing CIS (statistically significant in the multivariate analysis) implied cancer death in 90% of these patients. It can be assumed that apart from exophytic tumour, residual CIS was present in these cases.

One of the main objectives of this study was to establish whether DNA values measured with flow cytometry could help to predict cancer-free survival in patients with these advanced, mostly grade 3 tumours. Separating the tumours into diploid and aneuploid tumours did not give any additional information in this series with only 7 diploid

tumours. According to our earlier experience with a large number of cases, invasive grade 3 tumours are usually grossly aneuploid with a high proliferation rate (Tribukait, 1987). However, aneuploid tumours can be subdivided into tumours with one or several aneuploid cell populations. The occurrence of more than one aneuploid cell population was in this series significantly correlated with a reduced 5-year survival rate (15% versus 40% for those who had aneuploid tumours with one cell line). However, in the multivariate analysis ploidy did not have an independent power to predict cancer-free survival. Proliferation rate was of no value at all for further subdivision of the tumours in this series, which is in contrast to its known value otherwise (Tribukait, 1987).

One of the shortcomings of the present series is that bladder mucosa remote from the tumour was not examined in all cases. The impact of concomitant carcinoma *in situ* for radiosensitivity was, however, shown by the 21 patients fully examined: for these a strong correlation with multiple aneuploid cell populations and a high mortality rate of cancer was found. The existence of multiple aneuploid cell populations is in primary carcinoma *in situ* strongly correlated with progression to invasive disease (Norming *et al.*, 1991).

Radiotherapy, in the future perhaps combined with chemotherapy, is still an attractive form of treatment despite radical surgery with new techniques for bladder reconstruction. It is therefore worthwhile to continue to seek predictors of the outcome of therapy. Many patients in this series had been given radiotherapy because of old age,

Table 5 Cox Multivariate Analysis on Relative Survival

Factor	β	χ^2	P
Radiation response	2.74	63.9	<<0.001
Stage	0.58	10.2	0.001
CIS	0.76	5.8	0.016
Size	0.67	5.8	0.016

Other competing, non-significant factors, see Table 4

poor general health or advanced tumour stage. Some of the tumours responding to therapy were, at least in Sweden, the ones that in younger patients would have been operated on. It seems, however, that a thorough analysis of all prognostic factors prior to radiotherapy could predict the outcome in some way, making it possible to avoid major surgery not only in patients unfit for surgery.

Based on our findings, it can therefore be suggested that radiotherapy can be successful only in patients with less advanced tumours assessed according to stage and size, aneuploid tumours with only one aneuploid cell line, no carcinoma *in situ*, no ureteric obstruction, and in those patients for whom a complete transurethral resection of the exophytic tumour is possible.

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The Use of a Bladder Pressure Warning Device during Transurethral Prostatic Resection Decreases Absorption of Irrigation Fluid

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Summary—During a period of 4 weeks 102 patients underwent transurethral prostatic resection (TURP). Of these, 50 were randomly allocated to the use of an intravesical pressure device which warned the surgeon at a pressure elevation of 1.5 kPa. Ethanol (1%) was used as a marker in the irrigation fluid (glycine 2.2%), and absorption of ethanol-tagged irrigation fluid was detected by measurements in the expired air. In 28 patients absorption took place (in 8 of the 50 patients equipped with the warning device and in 20 of the 52 without the device). The greatest absorption was seen in the group without the device. No differences were found between the groups with regard to age, resected mass, resection time, resection speed, or haemorrhage. Patients who absorbed irrigation fluid were slightly older and bled more, and the resected mass was larger. The use of a pressure warning device reduces the amount of irrigation fluid absorbed and the number of patients who absorb irrigation fluid, and minimises the risk of the TUR syndrome.

It has long been known that irrigation fluid is absorbed during transurethral prostatic resection (TURP) (Creedy, 1947; Oester and Madsen, 1969; Rao, 1987). Absorption can occur regardless of whether the TURP is carried out by an experienced or an inexperienced urologist (Hjertberg *et al.*, 1991b). Large amounts of irrigation fluid may enter the systemic circulation very quickly. Absorption of more than 100 ml/min has been recorded at pressure gradients of 2.5 kPa between the pressure in the bladder (= prostatic fossa) and that in the iliac vein. We have also seen absorption of more than 200 ml/min at pressure in the bladder as low as 2.0 kPa (Hultén *et al.*, 1984).

Studies of absorption of irrigation fluid have until recently been hampered by the lack of a quick, simple and non-invasive method to be used routinely in clinical practice. During the past few years a method using ethanol as a marker of the irrigation fluid has been implemented in several Swedish hospitals (Hultén *et al.*, 1986). This method involves

the detection of absorption by measuring the ethanol in expired air. Irrigation fluid containing 2% ethanol was used initially, but later studies have shown that absorption of more than 200 ml can be detected by measuring the ethanol in expired air (Hahn, 1988; Hjertberg *et al.*, 1991a).

The surgical technique influences the absorption of irrigation fluid (Hahn *et al.*, 1990). It has also been proposed that a pressure warning device introduced suprapubically into the bladder could reduce the risk of absorption of irrigation fluid during the resection (Hultén and Ask, 1984).

The aim of the present study was to investigate whether the use of such a device does in fact reduce the absorption of irrigation fluid and the number of patients who absorb irrigation fluid.

Patients and Methods

Of 134 patients awaiting surgery for prostatic obstruction, and who underwent operation during November 1989, 102 agreed to participate in the trial. Glycin-Etanol® (glycine 2.2% and ethanol 1%; Travenol/Baxter) was used as irrigation fluid.

No patient with a previous history of alcohol abuse was included. The staff in the department of anaesthesiology randomly allocated the patients to the use of a pressure warning device. Fifty patients (Group I) were allocated to the pressure warning device and 52 were operated on without this device (Group II). A narrow suprapubic drain (Cystofix®, 10 F) was introduced into the bladder and attached to the pressure warning device (TURP Comfort, Rehab. Electromecanic AB, Boden, Sweden). The device is graded 0–7 kPa with an adjustable sound alarm from 0–7 kPa. The alarm was set to buzz at a pressure rise in the bladder of 1.5 kPa. The intermittent bladder emptying technique and a 24 F Storz resectoscope were used in all cases. In Group I the bladder was emptied as soon as the alarm sounded. In Group II the bladder was emptied at the discretion of the surgeon.

Spinal anaesthesia was used in most patients; a few had epidural block and 1 patient received inhalation anaesthesia.

Two experienced urologists performed all operations—52 and 50 patients each. There was no difference between the 2 surgeons with respect to patient age, operating time, resected mass of tissue, haemorrhage or resecting speed. They operated on 28 and 22 patients respectively, using the pressure warning device, and they both noted absorption of irrigation fluid in 14 patients. The surgeons used the same operating technique (Nesbith).

During the operation, end-expiratory breath samples were taken every 5 min using an Alcolmeter® model S-D2 (Gibb *et al.*, 1984) (Lions Laboratories Ltd, Barry, UK) which shows the values on a digital display in steps of 0.05% (1% = 0.1%) (from 0 to 9.95% w/w). The values were plotted against time. To allow a direct comparison between values in expired air and blood the ethanol concentration in air was converted into corresponding plasma concentrations, using the following factors: parti-

tion coefficient blood/air = 2100:1 (concentration in blood w/w), blood density 1.005 kg/l, water content in whole blood 86% (w/v). The technician was instructed to warn the surgeon when values exceeded 0.5%. The resecting and coagulation time (excluding in relevant cases cystoscopy, urethrotomy, lithotomy, introduction of indwelling catheter, *etc*) were recorded.

To estimate comparable absorbed amounts of irrigation fluid a rough integration of the time-ethanol curve was done. We used the product of the measured ethanol content in expired air and the actual measuring points (*i.e.* the product time × ethanol concentration in expired air).

The resected material was weighed to the nearest gram. The blood loss was estimated from the haemoglobin concentration in the irrigation fluid returning from the patient, using a modification of a simple photometric method (HemoCue AB, Helsingborg, Sweden) (Jansen *et al.*, 1978).

Student's *t* test and Fisher's exact test were used for the statistical evaluation.

Results

Details of the patients are given in Table 1. There were no significant differences between the 2 groups of patients with regard to age, resected mass, resection time, haemorrhage and haemorrhage per resected mass, or speed of operation (g/min). On histological examination 14 (14%) were found to have incidental prostatic cancer.

Absorption of irrigation fluid occurred in 28 patients (each surgeon 14 patients). Of the patients in Group II, 20/50 (40%) had ethanol in expired air. Three of these patients developed post-operative signs of the TUR syndrome with confusion and low serum sodium (124, 129 and 130 mmol/l). In 1 patient in Group II the operation was stopped

Table 1 Patient Data

	Total (<i>n</i> = 102) (mean ± SD)	Group 1 PWD (<i>n</i> = 50) (mean ± SD)	Group 2 No PWD (<i>n</i> = 52) (mean ± SD)	<i>P</i>
Age (years)	72 ± 7	72 ± 6	72 ± 7	NS
Resected mass (g)	27 ± 19	27 ± 17	28 ± 21	NS
Haemorrhage (ml)	381 ± 396	366 ± 385	394 ± 410	NS
Resection time (min)	29 ± 16	29 ± 14	30 ± 18	NS
Resection speed (g/min)	0.93 ± 0.39	0.94 ± 0.39	0.93 ± 0.39	NS

PWD = pressure warning device.

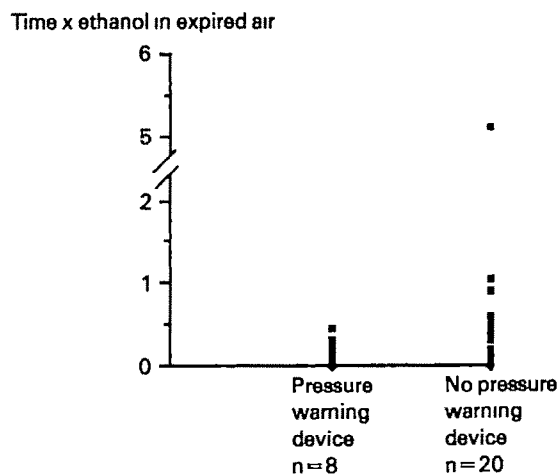


Fig. 1 The amount of absorbed irrigation fluid in the 2 groups expressed as time $\times$ ethanol in expired air.

after 15 min owing to a sudden increase in ethanol in expired air and at the same time large open veins were seen in the operation field. He had subjective symptoms including dizziness, paraesthesia of the face and slightly blurred vision. The patient recovered promptly after the operation. In only 8 of the 52 patients (15%) in Group I could ethanol be demonstrated in expired air. It is notable that the ethanol concentration in expired air rose to higher levels in Group II (Fig. 1). A plot of ethanol concentration in a patient absorbing irrigation fluid is shown in Figure 2.

The patients absorbing irrigation fluid had larger prostates and greater blood loss and were slightly older, but there was no difference with respect to the blood loss per gram resected mass. Resection speed was achieved slightly but significantly faster in the patients who absorbed irrigation fluid (Table 2).

The suprapubic catheter caused no complications. No patient required re-operation for post-operative haemorrhage.

A large number of operations were performed by the 2 surgeons during the month of the study. Therefore we analysed the data with the hypothesis that even experienced surgeons can increase their skill during a period of intense activity. Operating speed increased significantly during the first 2 weeks and then remained unchanged during the second 2 weeks (Fig. 3). There was no increase in haemorrhage per resected mass of tissue during the period.

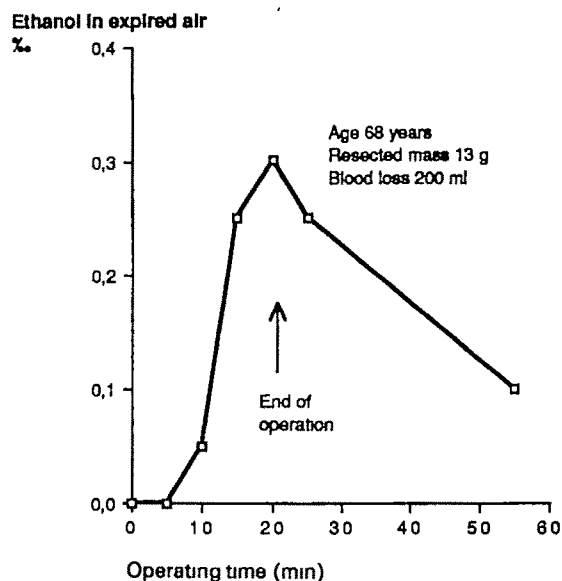


Fig. 2 Ethanol concentration in a patient absorbing irrigation fluid.

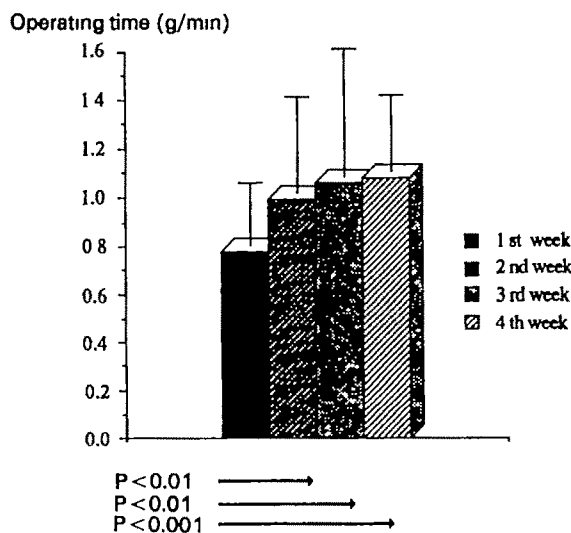


Fig. 3 Change in operating speed for 2 surgeons doing 102 transurethral prostatic resections in a 4-week period.

Discussion

The incidence and course of absorption have mainly been studied by determining the changes in serum sodium concentrations (Logie *et al.*, 1980; Rose *et al.*, 1981; Shearer and Standfield, 1981; Hahn, 1988). Other studies have used the measurement of plasma components (such as cholesterol, protein and acid phosphatase) (O'Donnell, 1984; O'Donnell *et al.*, 1986), radio-isotopes (Oester and Madsen,

Table 2 Comparison between Patients Absorbing and not Absorbing Irrigation Fluid

	All (n=102) (mean ± SD)	Absorbing (n=28) (mean ± SD)	Not absorbing (n=74) (mean ± SD)	P
Age (years)	72 ± 7	75 ± 7	71 ± 6	0.006
Resected mass (g)	27 ± 19	35 ± 20	24 ± 18	0.010
Haemorrhage (ml)	381 ± 396	526 ± 442	326 ± 366	0.022
Resection time (min)	29 ± 16	34 ± 18	27 ± 15	0.079 NS
Resection speed (g/min)	0.93 ± 0.39	1.08 ± 0.49	0.88 ± 0.33	0.015
Haemorrhage/ resected mass (ml/g)	13 ± 9	15 ± 7	12 ± 10	0.158 NS

1969; Hultén *et al.*, 1984), biochemical investigations of irrigation fluid in plasma (Logie *et al.*, 1980; Zucker and Bull, 1984; Norlén *et al.*, 1986a,b), regular interval monitoring (Hahn *et al.*, 1988) and transthoracic impedance changes (Cathely *et al.*, 1981) as indicators of fluid absorption. Most of these studies include an invasive method where a blood sample has to be taken and sent to the laboratory, and the result may take some time. As absorption takes place very quickly, the surgeon has to know immediately when it occurs in order to take the right precautions against further absorption. Monitoring of differences in irrigation fluid entering and leaving the bladder entails measuring large volumes in buckets, with the risk of spillage while emptying the bladder, leakage of resectoscope, and correction for blood loss and urine production often is not done. The regular interval monitoring (RIM) method described by Hahn (1988) gives more accurate results of fluid absorption, but is very time-consuming. Trans-thoracic measuring of impedance seems unreliable and the results are difficult to interpret at the moment. Therefore we feel that using ethanol-tagged irrigation fluid and measuring ethanol in expired breath as a result of absorption is the simplest and quickest method. The disadvantages are the kinetics of ethanol and the fact that absorption of irrigation fluid is not linear, which makes it difficult to translate exactly the ethanol content in expired air to absorption in ml. An empirical formula has been put forward by Hahn (1989):

$$\text{absorption (ml)} = 160 + 3210 \text{ ethanol in expired air (\%)}_0$$

and can be used as a rule of thumb. This means that approximately 480 ml of irrigating fluid have been absorbed at 0.1% ethanol in expired air, but also that 160 ml are absorbed at zero. We are investigating better formulas.

Leakage of irrigation fluid to the tissues around

the prostate and bladder gives a delayed reading on the Alcolmeter®.

The main finding was that with the use of a pressure warning device, both the amount of absorbed irrigation fluid (measured as the time-ethanol product) and the number of patients who absorbed irrigation fluid were reduced. Nevertheless, some patients absorbed irrigation fluid even when the device was used, probably because irrigation fluid enters the circulatory system even at very low pressure gradients between the surrounding prostatic veins and the operation field. Another explanation could be the "punctured balloon effect" in which the pressure gradient probably drops sharply after a perforation of sinusoids or the capsule and establishes the conditions for absorption of irrigation fluid.

Among patients absorbing irrigation fluid the prostates were bigger and the age higher. It seems clear that the bigger the prostate the greater the risk of absorption (Hjertberg *et al.*, 1991a, b), and elderly men have statistically bigger prostates.

The resection speed was greater in patients who absorbed irrigation fluid. It is often easy to work fast with the larger prostates, but these tend to leave a lining of bleeding sinusoids and more perforations of the capsule, providing conditions for absorption. The haemorrhage per resected mass was the same in the 2 groups, indicating that no technical problems arose in the patients who absorbed irrigation fluid.

It is interesting to note that even fairly experienced resectionists can significantly increase their operating speed. It might be assumed that the faster operating speed could lead to negligence, with tolerance of greater bleeding and a smaller mass of resected material, but the present study shows that this is not the case.

We conclude that the introduction of a pressure warning device in the bladder during TURP reduces the risk of absorption of irrigation fluid and

also the number of patients who absorb irrigation fluid. Nevertheless, approximately 1 in 6 patients absorbed fluid and we therefore recommend the ethanol method as a basis for measuring the amount absorbed. Performing many transurethral prostatic resections during a short period of time increased the operating speed even among experienced resectionists.

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Eosinophilic Prostatitis and Prostatic Specific Antigen

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Summary—Eosinophilic prostatitis is a rare form of abacterial prostatitis with uncertain aetiology. Its clinical presentation, like other types of abacterial prostatitis, commonly mimics carcinoma of the prostate. Transrectal ultrasound may be helpful in the diagnosis of prostatitis but histological confirmation is necessary. Prostatic specific antigen has been widely used in the diagnosis and follow-up of patients with prostatic carcinoma. High levels of this antigen ($> 30 \mu\text{g/l}$) have been claimed to be highly specific for prostate cancer, although lesser elevations may also occur in patients with large benign prostate glands and in bacterial prostatitis. We report 3 patients with histologically proven eosinophilic prostatitis and high levels of prostatic specific antigen. This diagnosis may closely mimic carcinoma of the prostate and must be excluded by histological examination of biopsy material before treatment for presumed prostate carcinoma is initiated.

Eosinophilic prostatitis (or allergic prostatitis) is a rare condition that may develop in the course of certain allergic disorders and may be associated with long-standing asthma (Thackray, 1978). The age at first presentation is similar to that of prostatic carcinoma. Eosinophilic prostatitis may present with sudden onset of difficulty in micturition or urinary retention, with no obvious past history of outflow obstructive symptoms. The findings on rectal examination are usually indistinguishable from those associated with carcinoma of the prostate. The prostate may feel irregular, firm or hard, may be normal in size or enlarged, and may have variable degrees of tenderness. Transrectal ultrasound (TRUS) may be helpful in diagnosing prostatitis (Doble and Carter, 1989) but is rarely diagnostic for eosinophilic prostatitis. Ultrasonic features include high density and mid-range echoes, echo-lucent zones, capsular irregularity and thickening.

Prostatic specific antigen (PSA) is now accepted as a useful tumour marker for the diagnosis and follow-up of prostatic cancer (Stamey and Kabalin, 1989) and some centres advocate its use for population screening of this tumour (Murphy, 1989;

Teillac *et al.*, 1990). It has higher sensitivity and specificity than prostatic acid phosphatase (Morote *et al.*, 1988; Van Dalen *et al.*, 1988), although the degree of sensitivity and specificity depends on the cut-off point between normal and abnormal values (Leitenberger and Altwein, 1990). A high cut-off point for PSA usually gives rise to higher sensitivity and specificity for prostatic carcinoma (Van Dieijen Visser *et al.*, 1988). Values exceeding $30 \mu\text{g/l}$ are claimed to give high sensitivity for prostate cancer and are also indicative of locally advanced or metastatic disease (Ercole *et al.*, 1987; Bordes *et al.*, 1989).

We report 3 patients with high PSA levels ($> 30 \mu\text{g/l}$) who subsequently were found to have eosinophilic prostatitis (Table). The serum PSA levels were measured by the Hybritech Tandem R immunoradiometric assay and our laboratory reference range for normal is 0 to $4 \mu\text{g/l}$.

Case Reports

Case 1. A 55-year-old man presented with a 2-day history of increasing difficulty with micturition leading to acute retention and a 4-day history of "flu-like" symptoms with generalised aches and pains. He had no previous history of bladder outflow obstructive symptoms. He was apyrexial. Clinical examination confirmed acute reten-

Table PSA Levels before and after Surgery

	Patient	Age (years)	Symptoms	Prostatic specific antigen	
				Pre-op. level ($\mu\text{g/l}$)	Post-op. level ($\mu\text{g/l}$)
Case 1	T.F.	55	Retention	36	<2
Case 2	M.R.	63	Poor flow	35	11
Case 3	G.B.	64	Retention	59	4.9

tion of urine and he was catheterised. Rectal examination revealed a moderately enlarged, firm and non-tender prostate. Urine cultures were negative. His serum PSA was $36 \mu\text{g/l}$. TRUS of his prostate showed an enlarged gland ($5.1 \times 5.4 \times 4 \text{ cm}$) with a hypoechoic area 1 cm in diameter in the posterior gland. Transperineal ultrasound guided biopsies of this area with the Biopsy gun showed non-specific prostatitis with diffuse infiltration by eosinophils. Transurethral resection of the prostate was performed and histology of the prostatic tissues confirmed eosinophilic prostatitis (Fig.). Repeat PSA level 6 months later was normal ($<2 \mu\text{g/l}$).

Case 2. A 64-year-old man presented with acute retention of urine. He had had another episode of retention 5 years previously and had a successful trial without catheter with a maximum flow rate of 15 ml/s. He denied any urinary symptoms between the 2 admissions. Rectal examination after catheterisation showed an enlarged, firm prostate. Urine cultures were negative and the serum PSA was $59 \mu\text{g/l}$. He underwent TURP and eosinophilic prostatitis was diagnosed histologically. The PSA level

3 months later had dropped to $4.9 \mu\text{g/l}$ and he was discharged.

Case 3. A 63-year-old man presented with a short history of progressive difficulty with micturition, frequency, suprapubic discomfort and frank haematuria. Clinical examination revealed mild suprapubic tenderness and a moderately enlarged, smooth prostate on rectal examination. His maximum urinary flow rate was 4.3 ml/s. Urine cultures and cytology were negative. His IVU showed normal upper urinary tracts and a trabeculated bladder with moderate post-micturition residual urine. Serum PSA level was $35 \mu\text{g/l}$. Subsequent TRUS showed a hypoechoic area 1 cm in diameter over the right posterior gland. Transperineal biopsies of this area revealed inflammatory changes of prostatitis only. Subsequent endoscopic prostatectomy confirmed eosinophilic prostatitis. His PSA level had decreased to $11 \mu\text{g/l}$ 2 months later and he was asymptomatic.

Discussion

Since the discovery of PSA (a glycoprotein with a molecular weight of 33 kD) by Wang *et al.* (1982), its uniqueness to prostatic tissue is well established. Recently, there have been several reports of elevation of PSA in acute bacterial prostatitis (Dalton, 1989). It has been suggested that prostatic acinar cell disruption, with subsequent leakage of the antigen during the acute inflammatory process, is the mechanism behind this rise in serum PSA level. The extracellular released PSA was shown to be transported by neutrophils and macrophages from the prostate stroma to the serum. This is consistent with findings from immunohistochemical studies which showed confinement of PSA to the cytoplasm of prostatic acinar cells and ductal epithelium (Sinha *et al.*, 1987). Ultrastructural study of the localisation of PSA in benign and malignant prostatic tissues (Warhol and Longtine, 1985) has shown that PSA is localised within the endoplasmic reticulum, cytoplasmic vesicles and vacuoles, and the lumen of prostate glands. Consequently, any pathological process which causes prostatic cellular destruction can lead to a rise in serum PSA level. Digital rectal examination has been reported to be associated with a similar transient rise in PSA (Stamey *et al.*, 1987; Adjiman

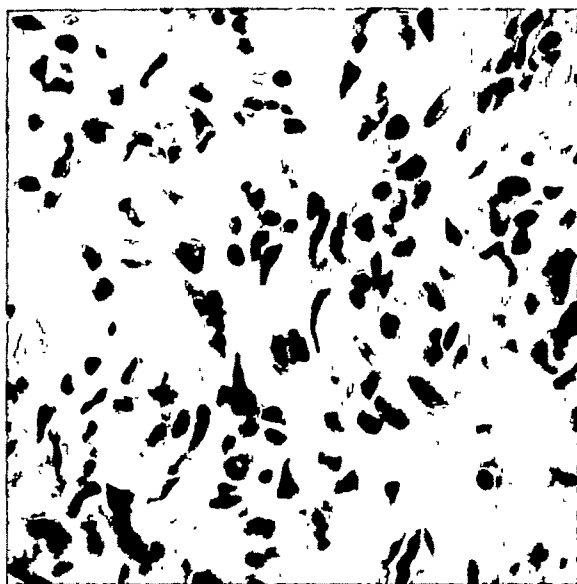


Fig. Histological section of prostate (case 1) showing prostatitis with granulomatous and inflammatory changes associated with eosinophilic infiltration. (H and E $\times 500$.)

et al., 1989). Prostatitis may also cause an elevation in PSA (Brawer *et al.*, 1989). Fuse *et al.* (1987) reported an 18% false positive rise in PSA due to prostatitis and Morote *et al.* (1989) showed elevation of PSA in 24% of patients with acute prostatitis and 3.3% of those with chronic prostatitis from a total of 1383 patients.

The association of eosinophilic prostatitis and raised PSA level has not previously been reported, although the mechanism of action appears to be similar to that of other forms of prostatitis. This is consistent with the microscopic finding of eosinophilic prostatitis, in which there are distinctive granulomas with central fibrinoid necrosis surrounded by histiocytes, multinucleate giant cells and dense infiltration of eosinophils (Thackray, 1978). Raised PSA levels may also be found in benign prostatic hyperplasia in direct relation to the prostate volume—0.3 µg/l/g (Stamey *et al.*, 1987). Our 3 patients all had acute urinary outflow obstruction (2 with acute retention) at presentation. Two patients had flu-like symptoms prodromally (consistent with eosinophilic prostatitis). In all 3 cases the PSA levels were measured at least 4 days after rectal examination. TRUS of the prostate in 2 cases showed hypoechoic areas which could have been confused with malignant foci. However, all 3 had histologically proven eosinophilic prostatitis. Each patient had raised PSA levels > 30 µg/l pre-operatively and these returned to nearly normal within 6 months post-operatively. It seems likely that the levels would have dropped spontaneously once the inflammatory process had settled, irrespective of the surgical intervention, which was necessary solely to relieve the outflow obstruction. These patients illustrate how closely eosinophilic prostatitis may mimic carcinoma of the prostate—high PSA level, a firm prostate and a hypoechoic focus on TRUS. Clearly this diagnosis must be excluded by core biopsy before treatment for prostatic malignancy is initiated.

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Disodium Pamidronate Identifies Differential Osteoclastic Bone Resorption in Metastatic Prostate Cancer

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Summary—In a controlled trial the effects of the osteoclast inhibitor disodium pamidronate were studied over a 6-month period in men with metastatic bone disease from prostate cancer. Using serial biochemical measurement of metabolic bone activity, and complementary subjective and quantitative bone histology, the effects of pamidronate were evaluated in tumour-free and metastatic regions of the skeleton, enabling analysis of the differential mechanisms of bone destruction in this disease.

Following treatment, abnormally high markers of bone breakdown fell significantly (fasting urine hydroxyproline/creatinine (OHP): $P < 0.05$; fasting urine calcium excretion (Ca_E): $P < 0.0001$), confirming that activated osteoclasts play an integral role in the osteolytic process. Serial histomorphometry of bone from tumour-free areas showed that pamidronate restored abnormal levels of bone erosion to normal in 93% of cases. Suppression of bone destruction was also evident within metastases, although this was incomplete.

The results confirm that osteoclast overactivity is responsible for a significant proportion of the accelerated osteolysis seen in both tumour-free and infiltrated bone in patients with prostate cancer. The differential effects in tumour-free and infiltrated bone suggest that the mechanisms of osteoclast activation may differ in metastatic and non-metastatic regions of the skeleton.

Prostate cancer, traditionally identified by osteoblastic skeleton dysfunction (Milch and Changus, 1956), is increasingly recognised as being associated with erosive and resorptive change in patients with disease metastatic to bone.

Histological studies of affected vertebrae (Galasko, 1976), analysis of urinary markers of bone breakdown (Percival *et al.*, 1987) and histomorphometric examination of both tumour-bearing (Charhon *et al.*, 1983; Urwin *et al.*, 1985) and tumour-free (Urwin *et al.*, 1985) skeletal biopsies have confirmed that a widespread destruction of

osseous tissue occurs as part of the neoplastic process. Physiological adjustment of parathyroid hormone (PTH) levels in response to calcium demand from metastases is a mechanism which has been implicated to explain erosive change identified in bone remote from tumour deposits (Charhon *et al.*, 1985; Urwin *et al.*, 1986) but within metastases it is unclear whether resorptive activity occurs as a result of direct tumour invasion (Galasko, 1976) or is mediated by osteoclasts, as has been proposed both in animals (Pollard and Luckert, 1985; Nemoto *et al.*, 1988) and humans (Galasko, 1976).

To determine the nature, site and mechanism of the resorptive process more precisely, disodium pamidronate, a potent inhibitor of osteoclasts (Fleisch, 1983), was administered to a group of patients with metastatic prostate cancer and its

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effect on skeletal function was compared with that in a similar but untreated group, by measurement of standardised serum and urine markers of metabolic bone activity and by quantitative and subjective histological analysis of tumour-bearing and tumour-free bone.

Patients and Methods

The study group comprised 42 patients with biopsy proven prostate cancer and metastatic bone disease on bone scan. Hormone manipulation by subcapsular orchiectomy or luteinising hormone-releasing hormone analogue therapy had been undertaken at least 6 months previously in all patients (median 19 months, range 6–91). Subjects were drawn from urological clinics with the same referral and treatment regimes: ethical considerations determined that patients receiving pamidronate were treated in separate clinical locations from those receiving no additional treatment. Of the 42 patients recruited, 27 were treated with intravenous pamidronate (30 mg weekly for 4 weeks, then twice-monthly for 5 months) and 15 were assessed over a similar duration without bisphosphonate therapy. Throughout the study no additional anti-cancer therapy was administered and oestrogens were not used at any time.

In both groups biochemical measurement of metabolic bone activity was carried out immediately before and monthly throughout the trial by means of serial assay of alkaline phosphatase and osteocalcin and fasting morning urine hydroxyproline/creatinine ratio (OHP) and calcium excretion (Ca_E) (Nordin *et al.*, 1976). Patients also underwent transiliac trephine core bone biopsies immediately before and after 6 months' treatment, to enable quantitative and subjective histological analysis of the effects of pamidronate on tumour-free and metastatic bone. Patients were "double labelled" with oral tetracycline before each procedure (250 mg qds for 3 days repeated after 10 days) for measurement of the bone mineralisation rate and biopsies were carried out under local anaesthesia. One or more transiliac bone cores were taken at each biopsy, samples being taken from both tumour-free and metastatic regions. Specimens were fixed in alcohol, resin embedded and sectioned undecalcified to facilitate standardised histomorphometric quantification using microscopic line intersect and point counting techniques with a Merz eyepiece graticule (Merz and Schenk, 1970). Cancellous bone surfaces were analysed to determine the extent of bone surface erosion (eroded

surface), the amount of osteoid produced by osteoblasts (osteoid surface and volume) and the amount of bone matrix in cancellous bone (trabecular bone volume). Further histomorphometric measurement was undertaken using a calibrated eyepiece graticule in crossed polarised light for determination of the thickness of the basic structural units of bone (mean wall thickness (MWT)) (Meunier, 1983), then in fluorescent light for measurement of the rate of bone mineralisation (the mineral apposition rate (MAR)) (Frost, 1976). Undecalcified and decalcified bone specimens from metastases were also analysed histologically for evidence of osteoclast activity and changes in cellular morphology and bone structure before and after pamidronate therapy.

Sequential biochemical values were analysed using a repeated measures analysis of variance. Values for osteocalcin, OHP and Ca_E required $\log_e$ conversion for data normalisation, values for alkaline phosphatase were normalised by $1/\sqrt{y}$ conversion and analysis of serum corrected calcium was carried out on simple mean values.

Histomorphometric data were compared before and after treatment and between groups using analysis of variance of simple mean values, with the exception of those for eroded surface, which were normalised by $\log_e$ conversion.

Results

Throughout the study there were no adverse effects from pamidronate treatment. Four treated patients died within the 6 months; deaths occurred at 3, 4 and 5 months (1, 1 and 2 patients respectively) and 1 patient withdrew (too ill to continue) after 5 months. Four control patients died during the same period (at 3, 5 and 6 months (2, 1 and 1 respectively)). All deaths were the result of advancing prostate cancer.

Alkaline phosphatase and osteocalcin were elevated at the outset (Fig. 1), a finding consistent with osteoblastic overactivity. Levels remained high in untreated patients but were lowered overall following pamidronate treatment (alkaline phosphatase: $P=0.014$; osteocalcin: $P=0.0006$). Biochemical markers of bone destruction are shown in Figure 2. In untreated patients the mean OHP rose significantly with time, whilst in the pamidronate group the overall trend in OHP was down, with mean levels significantly lower than in treated patients ($P<0.05$). The decrease in OHP levels did not occur universally: 6 of the 27 patients had a rising trend despite pamidronate treatment. The

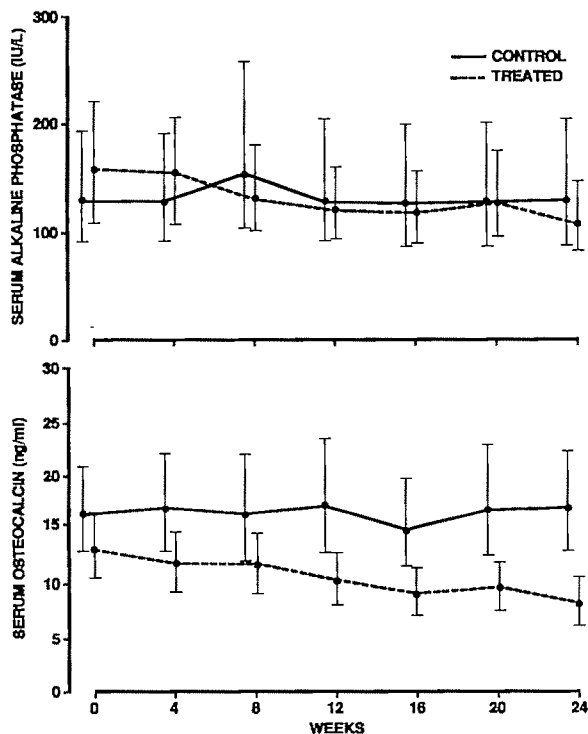


Fig. 1 Detransformed mean values and 95% confidence limits (following $\log_e$ (osteocalcin) and $1/\sqrt{y}$ (alkaline phosphatase) transformation for data normalisation). Osteocalcin and alkaline phosphatase levels were significantly lower following 3 months' treatment with pamidronate ($P > 0.01$ and $P = 0.014$ respectively). Levels in controls were unchanged throughout.

trend in Ca_E levels in untreated patients was similar to that for OHP, remaining steady or rising with time, but Ca_E was uniformly lowered in the pamidronate group ($P < 0.0001$), all patients exhibiting a diminution in urinary levels notwithstanding the trend in OHP. Changes in urinary calcium did not significantly affect the serum corrected calcium levels, which remained within the normal range in both groups.

Bone tissue from repeat tumour-free biopsies was available from 9 untreated and 14 pamidronate-treated patients. Failure to obtain repeat tumour-free specimens was due to death or withdrawal (9), biopsy failure (2) or tumour infiltration in 1 or more specimens (8). The histomorphometric indices are shown in the Table. These confirm a rising trend in eroded surface and a falling trend in bone volume in untreated patients. The increase in erosion was a consistent finding in the control patients but differences in levels before and after treatment did not reach statistical significance. The abnormally high eroded surface seen in both groups at the

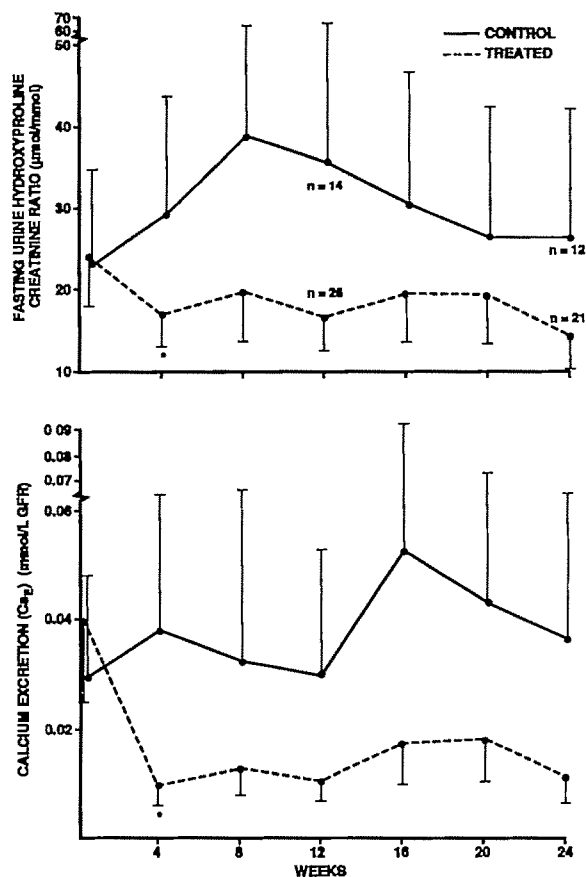


Fig. 2 Detransformed mean values and 95% confidence limits (following $\log_e$ transformation for data normalisation) for fasting urine hydroxyproline/creatinine (OHP) and calcium excretion (Ca_E). OHP levels rose significantly by 8 weeks in controls but fell in patients receiving pamidronate ($P < 0.01$). OHP levels were lower throughout following initiation of bisphosphonate treatment ($P < 0.05$). Ca_E levels fell significantly by 4 weeks following pamidronate and remained lower than controls thereafter ($P < 0.0001$). Figures denote the number of surviving patients at each time point. (Upper limit of normal for OHP = $19 \mu\text{mol}/\text{mmol}$)

outset was normalised by pamidronate but this was associated with a fall in the bone volume (in conjunction with a fall in all of the measured parameters of osteoblast function). Prior to study, bone tissue was obtained from metastatic regions in 10 patients. There was evidence of increased bone destruction in all biopsies, although the degree of destruction varied from specimen to specimen. In all specimens a proportion of the bone destruction was undertaken by flattened, active osteoclasts (Fig. 3A) and in some specimens by dark staining cells of indeterminate type. Tumour cells were also visible in close relation to areas of bone destruction,

Table Histomorphometric Indices for Tumour-free Bone before and after the Study

Mean values (normal)	Pamidronate (n=14)		Control (n=9)	
	Before study	After study	Before study	After study
Osteoid surface ($16 \pm 2.4\%$)	9.9 (7.8–12.1)	4.0 (1.9–6.2)	9.0 (6.4–11.6)	8.8 (6.2–11.4)
Osteoid volume ($1.6 \pm 0.3\%$)	1.8 (1.4–2.4)	0.5 (0.01–0.9)	1.2 (0.7–1.8)	0.8 (2.3–1.4)
Eroded surface ($4.1 \pm 0.6\%$)	7.1 (5.6–9.0)	3.7 (2.9–4.6)	7.5 (5.6–10.0)	8.6 (6.5–11.6)
Bone volume ($17.8 \pm 4.3\%$)	21.2 (17.8–24.5)	17.4 (13.9–20.9)	18.6 (14.4–22.7)	15.8 (11.7–20.0)
Mean wall thickness (μ)	29.0 (27.8–30.2)	24.2 (22.9–25.4)	28.1 (26.6–29.6)	28.4 (26.9–29.8)
Mineral apposition rate ($0.6–0.7 \mu/\text{day}$)	0.59 (0.54–0.64)	0.48 (0.35–0.53)	0.47 (0.41–0.52)	0.47 (0.41–0.52)

Surface erosion decreased significantly following pamidronate ($P=0.005$), as did all osteoblastic indices (osteoid surface, osteoid volume, mean wall thickness and mineral apposition rate) ($P=0.008, 0.04, <0.0001$ and 0.001 respectively). Bone volume also fell in both groups over the study period ($P=0.005$).

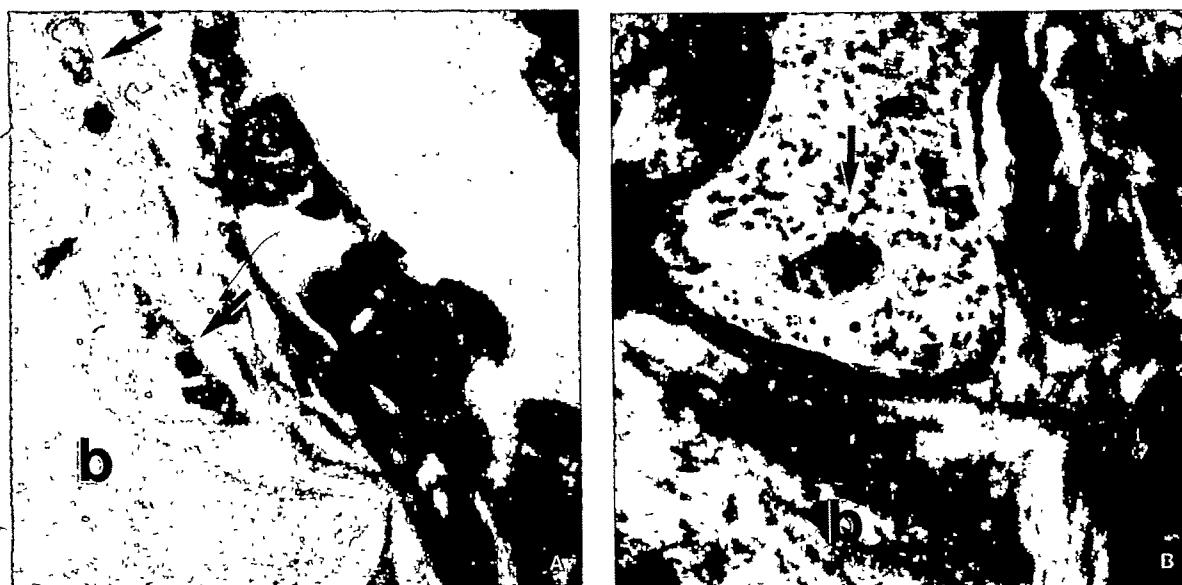


Fig. 3 Prostatic bone metastasis before (A) and after 6 months' pamidronate treatment (B). (A) Prostate cancer cells (dark staining) stimulate flattened, active osteoclasts (arrowed) to resorb bone from the surface of a trabeculum of cancellous bone (b). (B) Osteoclast (arrowed) showing a typical "post-pamidronate" effect. The cell is rounded, has increased nuclearity and rests in the marrow space away from the bone surface (b).

raising the possibility that tumour cells themselves may be responsible for a proportion of the observed osteolysis.

Biopsies through metastases were available from 7 patients following a 6-month period of pamidronate treatment. Ongoing derangement in bone metabolism was visible in all specimens but in 4 there was evidence of significant osteoclast inhibition. This was characterised by increased nuclearity and "rounding" of osteoclasts, with centralisation of the nuclei (Fig. 3B). The cells were usually seen lying separate from the bone surface, an appearance in keeping with impaired resorptive capacity (Plasmans *et al.*, 1980). This was not an "all or none" phenomenon: despite numerous morphologically deranged osteoclasts in some specimens there was always evidence of active osteoclastic resorption within the biopsy. In the remaining 3 biopsies persistent osteoclastic bone resorption was visible with no discernible alteration in osteoclast morphology. In addition, in 3 biopsies there were areas in which tumour cells were in direct contact with sites of bone surface erosion, again raising the possibility of direct tumour-mediated bone destruction.

Discussion

The traditional view of prostatic carcinoma as a disease inducing only bone formation within metastases has receded in the light of evidence confirming its bone resorbing tendency (Galasko, 1976; Charhon *et al.*, 1983; Urwin *et al.*, 1985; Percival *et al.*, 1987). In this investigation the effect of osteoclast inhibition on bone breakdown was studied in patients with metastatic bone disease, enabling evaluation and differentiation of the cellular mechanisms of osteolysis in prostate cancer.

Patients in the study were recruited from and treated in separate clinics as it was considered desirable to keep the 2 arms of the trial apart in order to avoid the need for placebo infusion in the control group of elderly men. Although this protocol led to an imbalance in the size of the 2 groups, the random pattern of patient referral and the similar therapeutic regimes for the primary cancer justified a controlled comparison of the 2 groups with and without pamidronate treatment.

At the outset of the trial, levels of urinary OHP were increased in both groups of patients, showing that bone resorption was pathologically high prior to investigation. In control patients, markers of bone breakdown showed a rising trend, in keeping with a progressive increase in the degree of bone

destruction as the disease advanced: this overall trend was reversed in the pamidronate group, showing that a proportion of the osteolysis was produced by osteoclasts.

In the tumour-free bone, measured levels of surface erosion were increased in both groups at the beginning of the study; this decreased to normal following pamidronate therapy and must, therefore, have been the result of osteoclast overactivity. The increased osteoclast drive is possibly due to homeostatic mechanisms to maintain normal serum calcium levels in the face of increased demand for calcium within osteoblastic metastases and indeed, elevations in circulating PTH and vitamin D have been reported in this condition (Charhon *et al.*, 1985; Urwin *et al.*, 1986). The universal downward shift seen in urinary Ca_E following pamidronate therapy would be consistent with this hypothesis, occurring as a result of increased renal tubular calcium conservation. This would compensate for the decrease in the liberation of ionised calcium from bone, thereby maintaining stable serum calcium levels. The other possibility is that the erosion may be due to occult, circulating, tumour-generated factors promoting accelerated osteoclast overactivity (a phenomenon known to occur in other malignant conditions (Mundy, 1988)). Whatever the mechanism, the response in the tumour-free bone was evidently different from that seen within metastases, since erosion was maintained to a greater or lesser extent in areas of malignant infiltration following pamidronate (*vide infra*).

The implications of a prolonged increase in tumour-free bone resorption are reflected in the downward trend in tumour-free volume with time, which suggests that the long-term effect of the increased erosion is chronic bone wasting (a condition which has been seen radiologically in metastatic prostate cancer (Hosking *et al.*, 1975)). Although the measured fall in bone volume was relatively small in the control group, it is important to note that the subset of patients with repeat tumour-free bone biopsies represent the milder end of the spectrum of disease in that they have survived 6 months and their tumour load is sufficiently light to enable consecutive sampling of bone not affected by malignant infiltration. It is therefore possible that the bone wasting effect is greater as the tumour load increases. It should also be noted that the bone volume decreased in the pamidronate-treated patients. However, the cause of this was evidently quite different, resulting from a decrease in osteoblastic anabolic activity (as shown by the diminution in the biochemical and histomorphometric

indices of osteoblast function). This effect is likely to be the result of pamidronate treatment itself; it has been shown that bisphosphonate drugs themselves have a direct anti-osteoblast effect (Stronski *et al.*, 1988).

The relatively small number of repeat biopsies through areas of tumour infiltration precluded direct histomorphometric comparison of regions affected by tumour, but within metastases osteolysis was always more pronounced than that seen in tumour-free bone. This destruction increased with time, as shown by the progressive rise in OHP and Ca_E levels seen in the worst affected control patients. The fact that levels of erosion in tumour-free bone did not increase appreciably in this group over the same period shows that the observed increase in OHP levels must have been the result of progressive intrametastatic bone lysis.

The presence of active intra-metastatic osteoclasts, and their inhibition in conjunction with a fall in biochemical markers of bone destruction following pamidronate therapy, confirms that a proportion of the bone lysis associated with tumour infiltration is the result of osteoclastic overactivity. Osteoclast-mediated osteolysis has been observed in the early stages of tumour invasion in animals and man (Galasko, 1976; Pollard and Luckert, 1985; Nemoto *et al.*, 1988) and the results of this study show that this is also the case in established metastases. The cause of the osteoclast hyperactivity is unknown but it may be due to abnormal osteoclast stimulation by tumour-generated substances. Human prostate cancer cells are known to possess mRNA for epidermal growth factor (EGF) (Morris and Dodd, 1990), EGF and TGF α are produced by cultured prostate cancer cells (Connolly and Rose, 1990) and the prostate cancer cell line PC₃ is known to synthesise PDGF-like proteins (Sitaras *et al.*, 1988). EGF, TGF α and PDGF all have the ability to stimulate osteoclasts to resorb bone (Vaes, 1988) and it is possible that cytokines such as these are released by metastatic tumour cells, thereby inducing intrametastatic osteoclast-mediated bone lysis.

The histological evidence showed that ongoing bone destruction within metastases of pamidronate-treated patients was partly due to the failure of osteoclast inhibition. The reasons for this are not clear but they may include an innate resistance of some osteoclasts for pamidronate or the presence of a very powerful osteoclast drive as a result of pathological tumour stimulation. Such a stimulus must be different from that seen in tumour-free bone, since inhibition of erosion occurred consist-

ently in the tumour-free areas following pamidronate. The other possible cause for persistent and progressive bone destruction may be direct bone lysis by tumour cells themselves. Direct bone destruction of this nature has been shown to occur *in vitro* (Eilon and Mundy, 1978) and in this study there were areas in which tumour was in direct contact with eroded bone surface, a finding which has been described previously (Galasko, 1976). This may represent direct tumour-mediated osteolysis, although it is impossible to confirm or refute this definitively on the basis of this study.

It is concluded that skeletal metastases arising from prostate cancer are associated with major bone destruction and that the degree of destruction increases progressively with time. In the tumour-free skeleton, osteoclast-mediated bone erosion is pathologically high and may induce bone wasting. However, the degree of destruction is far exceeded by that occurring in bone infiltrated by tumour. Within metastases a significant proportion of the skeletal destruction is the direct result of tumour-driven osteoclastic overactivity. This is inhibited to a variable extent by the bisphosphonate disodium pamidronate, an effect which ultimately may decrease the bone-related morbidity in patients with metastatic prostate cancer.

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Stress Relaxation Phenomenon in the Healthy Female Urethra

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Summary—Following dilatation, urethral pressure declines over the next few seconds to a state of equilibrium. The stress relaxation parameter, $P_{10.5}$, was defined as the relative pressure decrease 0.5 s after dilatation, where the pressures at 0.1 s and at the new equilibrium were set to 100% and 0% respectively. $P_{10.5}$ was calculated from 171 urethral dilatations performed at each of 3 urethral sites of measurement in 10 healthy volunteers. It was found to be independent of the rate and size of urethral dilatation. It showed a fairly high reproducibility rate when repeated after 1 h and 1 week. $P_{10.5}$ was calculated to approximately 60% with no variation along the urethra. The parameter is assumed to be useful in evaluating urethral sphincter function. Although the method can be performed without special urodynamic equipment, the frequency response of the pressure measurement system must be adequate.

The main functions of the urethra are to prevent leakage during the storage phase and to serve as a compliant urinary conduit during micturition. Evaluation of urethral sphincter function has been mainly indirect by pressure measurements during rest or stress episodes. Although a large number of parameters have been recorded, they are all of limited value in differentiating between normal and pathological sphincter function; in particular, they are not very helpful in determining the pathogenesis of inadequate sphincter function (Versi *et al.*, 1986). Direct assessment of the efficiency of sphincter function requires measurement of its resistance to dilatation. Such measurements can be performed by the technique used in this study, although a high degree of standardisation is a prerequisite. Intra-urethral pressure increases during rapid dilatation and decreases over the next few seconds to a new equilibrium pressure (Colstrup, 1984; Lose and Colstrup, 1990). Measurement of pressure and cross-sectional area (CA) during rapid dilatation equals in some way an *in vivo* length tension diagram of the circular urethral structures.

If the same pressure generating structures are stretched in different ways, resulting in different

pressure increments, the relative pressure decline is, however, expected to be unchanged in relation to time (Lose and Colstrup, 1990).

The aim of this study was to evaluate the relative urethral pressure decrease by time following rapid dilatation by assessing the influence of the size and rate of dilatation, the absolute degree of dilatation, the site of measurement, and to assess the reproducibility of the measurements.

Materials and Methods

The bladder and urethral pressure measurements were performed by a specially designed double microtip transducer catheter (Lose *et al.*, 1986). The tip sensor was uncovered. The urethral sensor was covered with a water-filled cylindrical rubber balloon, 1.5 cm long, mounted 5 cm from the tip. Inflation of the balloon in the required range gave pressure increases < 5 cm H₂O when it was placed in open air or water. Pressure recordings with the covered and uncovered sensors were checked in a pressure chamber and found to be identical. The rise time, the damping factor and the undamped frequency response of the pressure recording system have been found to be 0.0025 s, 0.6 and 189 Hz respectively (Lose *et al.*, 1986). The range of pressure measurement was 0 to 250 cm H₂O.

The CA was measured according to the field gradient principle over a segment, 2 mm long, in the middle of the balloon (Harris *et al.*, 1971; Colstrup *et al.*, 1983; Lose *et al.*, 1986).

The balloon was inflated with saline from 20 or 40 mm² to a maximum of 70 mm². The inflations were performed by a specially designed infusion pump driven by the gravitational force of a 2.2-kg weight. The speed of inflation was adjusted by interposing 1 of 3 tubes with fixed diameters between the pump and the infusion line connected with the balloon. Constant inflation rates of 45 and 150 mm²/s were obtained by the 2 smallest tubes, irrespective of the size of inflation or the urethral pressure. The largest tube gave increasing inflation rates from 150 to 300 mm²/s according to the amount of inflated saline due to a constant acceleration. The rate and size of CA induction were read from the tracings (Fig. 1).

The urethral pressure measured in the balloon was registered 0.1 and 0.5 s after inflation, ($P_{0.1}$) and ($P_{0.5}$) respectively, and at the new equilibrium pressure (P_{eqw}) after increase in the CA (Fig. 1). The relative pressure decrease from 0.1 to 0.5 s after inflation was expressed by a pressure-time parameter ($P_{10.5}$)

$$P_{10.5} = ((P_{0.5} - P_{eqw}) / (P_{0.1} - P_{eqw})) \times 100\%$$

The electromyography (EMG) signal from the pelvic floor was measured by surface electrodes placed at the mid-portion of the anterior vaginal wall to exclude striated muscle contraction during measurements (Lose *et al.*, 1987).

The CA, the pressures from the bladder and the balloon, and the EMG signal were registered,

processed and displayed on a 6-channel recording system (DISA URO-system 2100). The frequency response of the amplifying system was 100 Hz. A paper speed of 15 mm/s was used.

Ten healthy nulliparous women aged 21 to 45 years (median 25) without past or present urological or gynaecological complaints were examined in the supine position with an empty bladder. Urethral dilatations were performed with the middle of the balloon (the CA measuring segment) 0.75 cm from the bladder neck, in the high pressure zone, and 0.75 cm from the external meatus. The bladder neck was located by retraction of the catheter from the bladder with the balloon connected to a water reservoir at a height of 10 cm. A decrease in CA indicated the bladder neck. The catheter was retracted a further 0.75 cm, whereafter the total length of the balloon was placed in the urethra. The high pressure zone was located where the balloon connected to a water reservoir at a height of 100 cm showed the smallest CA. The distal site of measurement was located where the balloon was just visible at the external meatus.

At each site of measurement 4 to 6 inflations were performed with each of the 3 rates of inflation. The inflation was repeated with the greatest inflation rate after 1 h and after 1 week to evaluate the reproducibility.

The study was approved by the local scientific ethical committee and informed consent was obtained from all of the women.

Statistical significance ($P < 0.05$) was considered where 95% confidence interval of the difference calculated as $X_{\text{mean dif}} \pm (t_{2\alpha} \times \text{SEM})$ excluded 0.

Results

Figure 2 shows the overall results of $P_{10.5}$ calculated from 171 inflations at each of the 3 sites of measurement. The influence of the size and rate of dilatation on $P_{10.5}$ is presented in Figure 3. $P_{10.5}$ was unaffected either by the method of dilatation or by the absolute size of dilatation. The influence of the rate and size of dilatation was also analysed in individual women but no relationship could be established. Figures 2 and 3 demonstrate the homogeneity of $P_{10.5}$ at the 3 urethral sites.

The Table shows the reproducibility measured as the intra-individual variation of $P_{10.5}$ measured at intervals of 1 h and 1 week.

$P_{10.5}$ calculated from repeated measurement in 1 individual showed (in all of the women) a normal distribution.

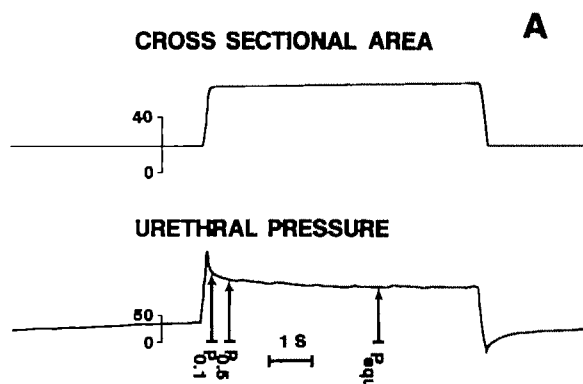


Fig. 1 Simultaneous measurement of pressure (cm H₂O) and CA (mm²) in the high pressure zone in a 28-year-old female. The pressures used in the calculation of $P_{10.5}$ [$P_{10.5} = (P_{0.5} - P_{eqw}) / (P_{0.1} - P_{eqw})$] are indicated

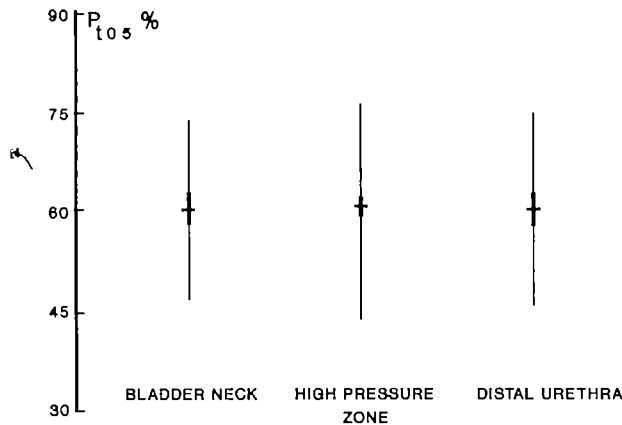


Fig. 2 $P_{10.5}$ obtained from 171 urethral inflations at each of 3 sites of measurement in 10 healthy young women. Horizontal bars indicate the mean of $P_{10.5}$; thick vertical bars indicate the 95% confidence interval of the mean; thin vertical bars indicate mean ± 2 SD

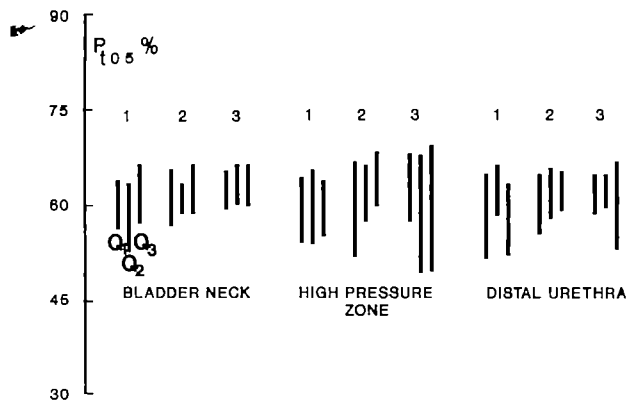


Fig. 3 $P_{10.5}$ obtained from measurements where the urethral dilatations were performed in different ways. Vertical bars indicate the 95% confidence interval; Q_1 , Q_2 and Q_3 indicate increasing dilatation rates from left to right (45, 150 and 150–300 mm²/s respectively); 1, 2 and 3 indicate change in urethral dilatation of ≤ 20 , 21–40 and ≥ 41 mm³ respectively.

Discussion

Intraurethral pressure increases during sudden dilatation and then declines in an exponential fashion over the next few seconds, according to the viscoelastic and muscular properties of the urethra (Colstrup, 1984; Lose and Colstrup, 1990). This pressure response, which corresponds to the elasticity described by Kondo *et al.* (1972), is highly correlated to the rate and size of the change of dilatation. The relative pressure decrease by time is described by a new parameter, $P_{10.5}$, which was found to be unaffected by the circumstances of urethral dilatation. $P_{10.5}$ showed a high degree of reproducibility when tested as the intra-individual

Table Reproducibility of $P_{10.5}$ in 10 Healthy Women

Site of measurement	Differences after 1 h	Differences after 1 week
Bladder neck	0 (–8 7)	–1 (–1 5)
High pressure zone	0 (–4 6)	–2 (–8 3)
Distal urethra	0 (–5 3)	1 (–5 8)

Values are differences between the initially obtained $P_{10.5}$ and after 1 h and 1 week. Values are means with 95% confidence intervals in parentheses.

variation from measurements performed at intervals of 1 h and 1 week. Consequently, $P_{10.5}$ is interpreted as a constant characteristic for a given urethra, or at least at 1 site of measurement, although there was no variation along the length of the urethra in the healthy women. $P_{10.5}$ showed a normal distribution when the measurements were repeated in one individual. Thus accuracy can be improved with several measurements in each subject.

The balloon (1.5 cm long) that was used to dilate the urethra was fully deformable and so accommodated to the urethra over that length. Because the CA measured at the mid-portion of the balloon did not change after inflation (Fig. 1), the pressure decrease can be considered uniformly distributed along the length of the balloon. Furthermore, a shorter balloon may not be able to influence the periurethral structures in the same way because of a higher degree of inner softness of the urethral wall (Zinner *et al.*, 1977).

In this study the pressure decrease from 0.1 to 0.5 s was used in the calculation of $P_{10.5}$. Because of the configuration of the curves and the influence of pulsations (Fig. 1) the relative pressure decrease during a fixed time was determined instead of a time constant for a relative pressure decrease (Lose and Colstrup, 1990). The 2 parameters, however, express the same. The accuracy of the pressures obtained 0.1 and 0.5 s after inflation can be considered acceptable (Rask-Andersen and Bergsten, 1982). The pressure spike at the end of dilatation was not used because of less accuracy in the determination of this parameter and because of the potential risk of interfering with balloon elasticity (Thind *et al.*, 1991).

Urethral dilatation adds energy to the periluminal structures. The subsequent dissipation of energy as seen by the pressure decrease (Zinner *et al.*, 1977) may be due to damped extension of non-contractile structures or to changes in length of muscle tissue (Little, 1969). An energy conserving

system such as strong muscle tissue with many slide filaments will tend to increase $P_{10.5}$, whereas connective tissue components will decrease it. Similarly, $P_{10.5}$ will be low at atrophy or denervation of the intra- and peri-urethral muscles and at fibrotic scarring of the urethra.

Although it is not possible to predict precisely which structures contribute to the pressure response at dilatation, it seems likely that the response is primarily generated by the striated muscles and collagen tissue in and around the urethra (Buchtal, 1949; Hill, 1950). The smooth muscles may be stimulated by stretching, resulting in a subsequent pressure increase after 0.5 to 1 s (Hill, 1950; Gordon and Siegman, 1971). This was not seen in the present study.

$P_{10.5}$ was unaffected by the degree of dilatation. Therefore it must be assumed that identical intramural and peritubular structures were stretched at varying degrees of dilatation in this study. Furthermore, the collagen fibres in the urethral wall must be arranged in such a way that a minimum number are stretched during dilatation; otherwise the compliance would have been low (Hickey *et al.*, 1982).

The finding of identical $P_{10.5}$ along the urethra may be related to the age and nulliparous state of the women. In addition, the sites of measurement were rather close to each other. However, in a study of the mechanical properties of healthy women no variation along the urethra was found (Lose, 1989).

In conclusion, $P_{10.5}$ is a constant characteristic of the viscoelastic and stress relaxation properties of the intra- and peri-urethral circular structures and is independent of the method of stress (induction of increasing CA). More data are required to determine its value in differentiating between pathophysiological conditions of the urethral sphincter, in assessing function before and after pelvic floor exercises, and in evaluating pharmacological treatment of sphincter insufficiency. The method is simple to perform. A prerequisite is a pressure measurement system with a frequency response high enough to measure the pressures at 0.1 and 0.5 s after dilatation (Rowan *et al.*, 1987). The pressure due to elastic properties of the balloon must be low; otherwise this should be included in the calculations.

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Urethral Stress Relaxation Phenomenon in Healthy and Stress Incontinent Women

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Summary—Urethral stress relaxation was induced by sudden forced dilatation. The stress relaxation parameter, $P_{10.5}$, was defined as the relative pressure decrease 0.5 s after dilatation, where the pressures at 0.1 s and at the new equilibrium were set to 100% and 0% respectively. $P_{10.5}$ was calculated in 28 healthy and 30 women with genuine stress incontinence. Measurements were performed at the bladder neck, in the high pressure zone and in the distal urethra. The measurements showed that all along the urethra, $P_{10.5}$ was statistically significantly greater in the healthy women than in the incontinent women, the greatest difference being found at the bladder neck. Although there was a slight overlap in values between the 2 groups, this parameter seems useful in differentiating between competent and incompetent urethral sphincters.

The urethral pressure increase which takes place during forced dilatation is followed by a pressure decrease or stress relaxation in an exponential fashion over the next few seconds, according to its viscoelastic properties (Colstrup, 1984; Lose and Colstrup, 1990; Thind, 1992). The pressure response to dilatation is an integrated reaction to stretch of the contributing intra- and peri-urethral anatomical structures, which are mainly arranged in a circular fashion. It has been shown that energy added by stretch is released faster from connective tissue than from muscle tissue (Kondo *et al.*, 1972; Kondo and Susset, 1974). Consequently, a strong sphincter with many sliding filaments may give rise to a slow pressure decrease, in contrast to a weak sphincter or a sphincter with increased connective tissue content (Fung, 1981). A method of evaluating urethral stress relaxation has been introduced by which the parameter $P_{10.5}$ describes the relative pressure decrease by time subsequent to the pressure increase provoked by forced dilatation (Thind, 1992). The aim of this study was to assess the value of the stress relaxation parameter in assessing urethral sphincter efficiency.

Materials and Methods

The urethral stress relaxation measurements were performed by a specially designed catheter mounted with a balloon (Thind, 1992). The balloon was inflated with saline by manual injection from a 1-ml syringe. The cross-sectional area (CA) was changed from 20 mm² to approximately 55 mm². The change in CA was read from the tracings (Fig. 1).

The urethral pressure 0.1 s and 0.5 s after inflation, ($P_{0.1}$) and ($P_{0.5}$) respectively, and at the new equilibrium pressure (P_{equ}) after increase in the CA, were used for the calculations (Fig. 1). The stress relaxation parameter, $P_{10.5}$, was calculated as the relative pressure decrease 0.5 s after inflation, where $P_{0.1}$ and P_{equ} were set as 100 and 0% respectively.

The electromyography (EMG) signal from the pelvic floor was measured by surface electrodes placed at the mid-portion of the anterior vaginal wall to exclude striated muscle contraction during measurements (Lose *et al.*, 1987).

The CA, the pressures from the bladder (tip sensor) and the balloon, and the EMG signal were registered, processed and displayed on a 6-channel recording system (DISA URO-system 2100). The

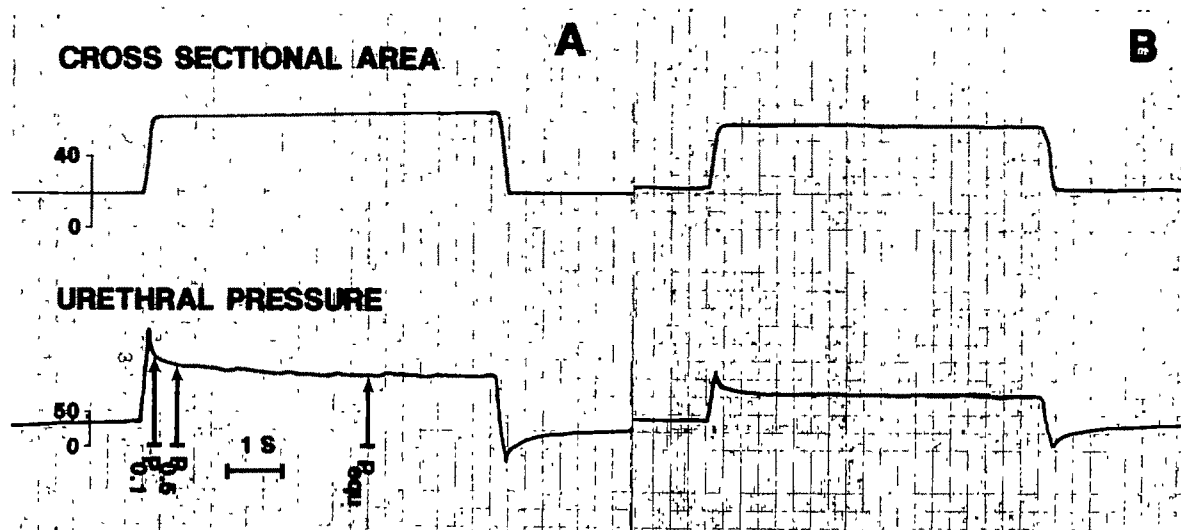


Fig. 1 Simultaneous measurement of urethral pressure (cmH₂O) and cross sectional area (mm²) during forced dilatation (A) Measurement at the bladder neck in a healthy 28-year-old female volunteer (B) Measurement in the high pressure zone in a 42-year-old stress incontinent woman. The pressures 0.1 s and 0.5 s after dilatation and at equilibrium were used for calculation.

frequency response of the amplifying system was 100 Hz. A paper speed of 15 mm/s was used.

A group of 28 healthy female volunteers without past or present urological or gynaecological complaints and 30 patients with genuine stress incontinence were included in the study. Clinical data are presented in the Table. In the healthy volunteers the pelvic examination was normal, urine culture was sterile and urinary flow rates were normal. A detailed history and urine culture were obtained from the patients, and urethral profilometry was obtained using the Brown-Wickham technique with an 8F single lumen catheter with 2 opposite

side holes. All patients demonstrated significant incontinence. At a 1-h pad weighing test (Lose *et al.*, 1988) the patients had a median urine loss of 9 g (range 0–77). The patients without significant leakage during the 1-h test demonstrated significant leakage (> 8 g/24 h) (Jørgensen *et al.*, 1987) during a 24-h pad weighing test. The condition of genuine stress incontinence was confirmed either by the observation of leakage produced by stress and/or by a positive pad weighing test in the absence of demonstrable detrusor instability on cystometry or significant residual urine.

The study was approved by the local scientific ethical committee and informed consent was obtained from all of the women.

The measurements were performed with the women in the supine position with an empty bladder. Urethral dilatation was performed with the middle of the balloon (the CA measuring segment) 0.75 cm from the bladder neck, in the high pressure zone, and 0.75 cm from the external meatus (Thind, 1992). With the balloon connected to a water reservoir the CA-measuring segment was secured within the urethra by squeezing, during which the urethral CA showed a reduction.

Statistical analyses comparing the 2 groups were performed using the Mann-Whitney test, and the Friedman test was used to compare the 3 sites of measurement in 1 group. $P < 0.05$ was considered statistically significant.

Table Clinical Data

	Healthy women (n=28) Median (range)	Stress incontinent women (n=30) Median (range)
Age (years)	43 (25–74)	49 (37–76)
Parity	2 (0–4)	2.5 (0–4)
Positive stress test	0	23
Cystocele	0	8
Previous incontinence surgery	0	0
Hysterectomy	0	5
MUCP (cm H ₂ O)	81 (30–120)	44 (20–76)

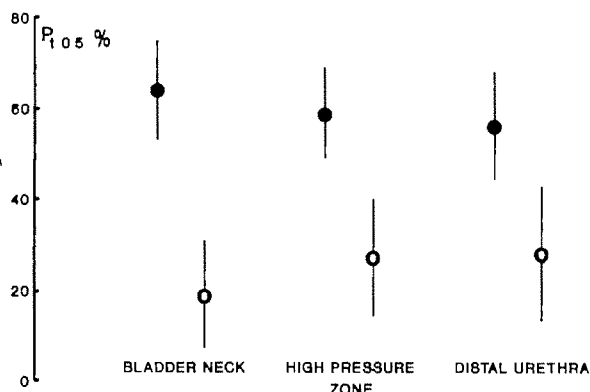


Fig. 2 $P_{10.5}$ calculated in 28 healthy female volunteers (•) and in 30 stress incontinent women (○). Values are mean $\pm$ SD.

Results

Figure 2 demonstrates the results of $P_{10.5}$ obtained at the 3 urethral sites in healthy and stress incontinent women. Along the length of the urethra $P_{10.5}$ was statistically significantly higher in the healthy women compared with the stress incontinent women. In the latter group the values at the bladder neck were statistically significantly lower than at the 2 other sites of measurement. In the healthy women the trend was reversed, *i.e.* there were higher values at the bladder neck than at the other sites, although this was not statistically significant. The difference between healthy and stress incontinent women was most pronounced at the bladder neck.

Neither in the healthy nor in the stress incontinent women could a correlation between $P_{10.5}$ and age be established.

In none of the groups did the EMG signal show any significant change during urethral dilatation.

Discussion

In this study a stress relaxation parameter, $P_{10.5}$, was obtained in healthy and stress incontinent women. It showed a statistically significant difference between the 2 groups along the entire length of the urethra, with the greatest difference at the bladder neck (Fig. 2).

The parameter $P_{10.5}$ delineates the relative dissipation of energy by time from the anatomical structures stretched by urethral dilatation (Thind, 1992). Accordingly, $P_{10.5}$ is closely related to the time constant of the same structures (Lose and Colstrup, 1990). Energy conserving structures such

as muscle tissue tend to increase $P_{10.5}$ in comparison with connective tissue, which reduces it (Kondo *et al.*, 1972; Kondo and Susset, 1974).

The stress relaxation recorded by this method, although an integrated reaction, is mainly a response to stretch of the circular structures in and around the urethra. Consequently, the contribution from the intramural connective tissue and smooth muscles can be considered sparse, as these are predominantly longitudinally arranged (Hickey *et al.*, 1982; Huisman, 1983). The horseshoe-shaped rhabdosphincter, on the other hand, with its abundant fibres in the middle two-thirds of the urethra, is arranged circularly and its contribution seems obvious (Gosling, 1985). However, from its uneven distribution along the length of the urethra a lower $P_{10.5}$ at the bladder neck was to be expected. Since the opposite was observed in healthy women, the additional peri-urethral structures probably have some influence on urethral stress relaxation. In this context it would be obvious to focus on the levator ani muscle, which acts through its ligamentous suspensions along the upper two-thirds of the urethra (Gosling, 1985; DeLancey, 1989).

The results of this study indicate genuine changes in the intra- and/or peri-urethral structures in patients with stress incontinence (Fig. 3). Applying an advanced mathematical analysis to the results may help to explain the structural changes, but that is beyond the scope of the present study (Kondo and Susset, 1974).

The fact that closure forces are weakened at rest and during contraction in stress incontinent patients correlates well with the results of this study

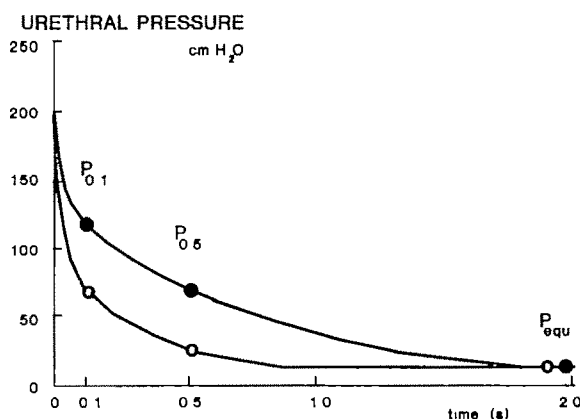


Fig. 3 Schematic illustration of urethral stress relaxation with pressure decay following forced dilatation in a normal (•) and an incompetent urethral sphincter (○).

(Enhörning, 1961; Lose, 1991). The finding of the greatest reduction of $P_{10.5}$ at the bladder neck in stress incontinent women confirms the results of other studies showing the most pronounced reduction in the active sphincter mechanism and the shortest recovery time at the bladder neck (Enhörning, 1961; Lose and Colstrup, 1990).

The small overlap in $P_{10.5}$ between the 2 groups, most pronounced at the distal urethra, may be related to the fact that genuine changes in stress incontinence are most pronounced in and around the proximal urethra. However, the pathogenesis of stress incontinence is complex and complete interpretation is impossible. The results in the 2 groups may be further improved by repeating the measurements, as normal distribution has been demonstrated intra-individually (Thind, 1992). In addition, a certain minimum size of the provoked pressure increase is necessary as the readings of the tracings may otherwise be difficult.

In patients where scarification due to surgical procedures, irradiation or inflammation can be omitted, a reduction in $P_{10.5}$ is believed to result from weakening of the sphincter muscles, either because of defects in the suspensory ligaments reducing the muscle impact on the urethra or because of partial denervation and/or muscle atrophy (Smith *et al.*, 1989).

$P_{10.5}$ seems to be a useful parameter for differentiating between competent and incompetent urethral sphincters; it appears to delineate genuine urethral changes as in stress incontinence, although more data are required before the method can be firmly established.

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Müllerian Duct (Prostatic Utricle) Cyst: Diagnosis and Treatment in Subfertile Males

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Summary—Müllerian duct cysts causing ejaculatory duct obstruction were discovered in 26 subfertile males; 21 patients had either azoospermia or very severe oligozoospermia. Characteristic seminal findings were a small volume ejaculate with acid pH and little or no fructose. The lesions were demonstrated by vasography and treated by endoscopic incision.

After surgery there was a distinct improvement in volume of the ejaculate and sperm concentration in 10 patients, although another 10 patients continued to have azoospermia or severe oligozoospermia due to either persisting obstruction or secondary epididymal blocks. Eight female partners became pregnant.

Englisch (1874) first described and illustrated a müllerian duct cyst, an embryological remnant lying between the ejaculatory ducts of wolffian origin and displacing them laterally. The condition appears to be a cystic dilatation of the prostatic utricle, a müllerian vestige normally present in males (Morgan *et al.*, 1979), composed of urogenital sinus and wolffian cells caudally and müllerian cells cranially (Glenister, 1962; Currarino, 1986). Examples of müllerian duct cysts being associated with infertility have been clearly illustrated by Brooks (1969), Stanley (1969), Hassler and Weber (1978) and Kerenyi and Erdei (1979). In each of these cases, incision of the müllerian duct cyst led to marked improvement in the sperm output with pregnancy in 3 of the 4 female partners concerned. Sharlip (1984) described 3 patients, 1 of whom achieved a normal sperm count after endoscopic incision with resulting pregnancy. In the second case (a previously vasectomised man) the sperm count remained zero, and the third patient elected not to be treated.

Recent collected review of our experience of ejaculatory duct obstruction in 87 subfertile males,

treated between 1976 and 1990, indicated that müllerian duct cyst was the underlying cause in 20%; following surgical treatment, fertility was restored to many of these men (Pryor and Hendry, 1991). This group therefore seemed worthy of further detailed study and our continuing experience is described in this report.

Patients and Methods

A group of 26 subfertile males aged between 23 and 44 years (median 31) had a history of infertility of 0 to 14 years' duration (median 3). The female partners were aged 20 to 37 years (median 30). Six were known to have been previously fertile, 6 had a history of epididymitis in the past, and 4 had previously complained of haemospermia.

All patients were fully investigated (Hendry *et al.*, 1973), including measurement of hormone levels (Pryor *et al.*, 1976). All had at least 1 normal-sized testis (>15 ml) and serum FSH which was either normal or only slightly elevated. The scrotum was explored under general anaesthesia and vasography was performed after injection of 3 to 5 ml of 25% or 45% Hypaque, using either direct puncture with a 25 gauge needle or incision and cannulation with a 2 F Portex cannula. The typical X-ray appearances of müllerian duct cyst are shown



Fig. Vasogram showing müllerian duct cyst.

in the Figure. Once the presence of the cyst was recognised, a few ml of 0.1% solution of methylene blue were injected into the vas and the scrotum was closed.

The patient was then placed in the lithotomy position and a cystoscope was passed. The müllerian duct cyst was sometimes hard to recognise, but was situated between the verumontanum and the bladder neck and could be made more easily visible by placing a gloved finger in the rectum and pressing the cyst forwards. The cyst was opened by incision of the verumontanum with the optical urethrotome. Entry into the cyst was recognised by the methylene blue dye gushing out. The incision was repeated if follow-up seminal quality failed to improve, and when necessary the roof of the cyst was removed by endoscopic resection. Following the operative procedure, a catheter was passed and the bladder was drained for 24 h. Antibiotic cover was given.

The patients were followed up by repeated seminal analysis and inquiry was made as to the occurrence of pregnancy in the female partners.

Results

The results of seminal analysis at presentation are shown in Table 1. Characteristically, the volume of the ejaculate was small (median 0.5 ml); pH ranged from 6.5 to 7.6, the median being low at 7.0. A total of 21 patients had either azoospermia or severe oligozoospermia (<1 m/ml).

At operation, the epididymes were noted to be distended in 19 patients and in 6 of these the epididymal tubules and vas were filled with old blood. The epididymes appeared normal in 3 patients and the appearance was not recorded in 4.

Table 1 Results of Seminal Analysis before Treatment (range + median values)

Volume (ml)	pH	Sperm concentration (m/ml)			
		0	<1	1–10	≥ 11
0.1–2.8 (0.5)	6.5–7.6 (7.0)	13	8	3	2

Testicular biopsies were normal on both sides in 19 patients, were normal on 1 side with atrophy on the other side in 3, and the results are not known in 4.

Endoscopic incision was carried out once in 17 patients, twice in 3 and thrice in 2 patients. The cyst appeared to rupture spontaneously following injection of the vasogram dye in 2 cases. In 4 patients epididymovasostomies were carried out for secondary epididymal blocks. Incision of the cyst was unsuccessful in 2 patients and sperm reservoirs were inserted (Brindley *et al.*, 1987).

The follow-up sperm counts are shown in Table 2. It may be seen that the average volume of the ejaculate improved, the median increasing to 2.1 ml. The sperm concentration improved markedly in 10 patients, although it will be noted that in another 10 patients azoospermia or severe oligozoospermia (<1 m/ml) persisted. Eight female partners became pregnant (overall pregnancy rate 31%).

Discussion

Routine vasography revealed ejaculatory duct obstruction in 5% of 370 azoospermic men with normal serum FSH levels undergoing scrotal exploration (Hendry *et al.*, 1990). The diagnosis may be suspected on clinical grounds. The finding of a small volume acid semen which does not contain fructose in such a patient in whom the vasa are palpable is virtually pathognomic. Unfortunately, the diagnosis may be overlooked for a number of

Table 2 Results of Seminal Analysis after Treatment (range + median values)

Volume (ml)	Sperm concentration (m/ml)			
	0	<1	1–10	≥ 11
0.5–5.2 (2.1)	7	3	5	9

reasons. Most patients are referred with a diagnosis simply of azoospermia or severe oligozoospermia, but without details of volume and chemical composition of the semen. Once these characteristic features are recognised, the diagnosis will be suspected. At surgical exploration the epididymes may not show the characteristic distension of tubules that is usually seen with obstruction. Furthermore, injection of fluid up the vas may be accommodated by the cyst without backflow. It follows that if this readily correctable condition is to be diagnosed, all patients with azoospermia or severe oligozoospermia must have the volume, pH and fructose content of the seminal fluid measured at the time of initial consultation and examination. If these are abnormal, transrectal ultrasound provides a non-invasive method of imaging the area (Takatera *et al.*, 1987; Carter *et al.*, 1989) and might usefully precede the scrotal exploration.

At the time of scrotal exploration, vasography should be carried out. If the X-ray shows the characteristic presence of the cyst (Fig.), it is helpful to inject a few ml of 0.1% solution of methylene blue dye up the vas to define the presence and boundaries of the cyst more clearly. An interesting feature is that the blue dye injected up one vas often descends down the opposite vas, indicating that both ejaculatory ducts must empty into the common cavity of the müllerian duct cyst. This phenomenon has also been noted by others (Elder and Mostwin, 1984; Sharlip, 1984).

Surgical correction of the abnormality is by endoscopic incision (Weintraube, 1980; Vicente *et al.*, 1983; Goldwasser *et al.*, 1985). This is facilitated by placing the patient in the lithotomy position with urological drapes to allow intra-operative digital examination *per rectum* so that the ejaculatory cyst contents can be expressed. The cyst may not be easily recognised and forward pressure from the gloved finger in the rectum may be necessary in order to visualise the cyst. It is usually relatively easy to enter the cyst in the midline using the optical urethrotome and characteristically the blue fluid gushes out once this has been done.

The results of surgery have not been universally successful. In 5 cases the cyst had to be incised again when a normal sperm count once again became negative. Repeat endoscopic examination revealed that the incision in the cyst had healed over and the cyst had recurred. In 2 patients the procedure had to be repeated on a third occasion, when the opportunity was taken to remove the roof of the cyst with a resectoscope.

A history of epididymitis is not uncommon in

these patients (Stanley, 1969) and 3 of our patients had atrophic testes on 1 side, presumably resulting from inflammatory damage. It is therefore not surprising that secondary epididymal obstruction may be present and may require epididymovasostomy (Silber, 1980). Blood is often seen in the epididymis and vas and a history of haemospermia is not uncommon. It is not clear where this blood comes from, although it has been reported by Fanous *et al.* (1982). Six of our patients were previously fertile, and so it appears that the outflow of the cyst may become obstructed and gradually fill up during adult life. In one case a marked change in the volume of the ejaculate was noted after an attack of haemospermia which was fully investigated, although no cause was defined.

The findings of this study emphasise the importance of considering the details of the results of seminal analysis in patients referred with azoospermia or severe oligozoospermia, and then examining the men carefully, supplemented by transrectal ultrasound whenever necessary. Vasography remains essential if the diagnosis of müllerian duct cyst is not to be missed in these subfertile males, an abnormality which is easily correctable by simple endoscopic incision.

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Treatment Decision for Stage I Non-seminomatous Germ Cell Tumours Based on the Risk Factor "Vascular Invasion"

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Summary—Surveillance has become an alternative treatment modality for stage I non-seminomatous germ cell tumours with reported relapse rates of up to 30% in retrospective studies. Results obtained in our retrospective study showed vascular invasion in primary tumours to be the risk factor with the highest negative predictive value. Since January 1985 patients with stage I non-seminomatous germ cell tumours have been stratified by the presence or absence of vascular invasion in the primary tumour: those without vascular invasion ($n=26$; group A) were subjected to a rigorous surveillance programme, while those with vascular invasion ($n=22$; group B) were given 2 chemotherapy courses of bleomycin, etoposide and platinum in the hope of preventing progression. Relapse rates were 3.8% and 9% in groups A and B, respectively. The pooled relapse rate for both groups A and B ($n=48$) was 6.2% (3/48). After a mean follow-up time of 36 months 95.8% (46/48) of the patients were without evidence of disease.

For many decades a standardised management concept was used for non-seminomatous germ cell tumours stage I (NSGCT I): radical or limited retroperitoneal lymphadenectomy. As the outcome obtained was excellent, there was little need for modifying this successful concept. Consequently, surveillance programmes were started late, *i.e.* in 1979 in both the UK and the USA (Peckham *et al.*, 1982; Johnson *et al.*, 1984; Javadpour, 1986). Relapse rates were reported to be between 17 and 33% (Table 1). While all of the patients were cured by aggressive chemotherapy, the surgery-related morbidity the patients were spared had to be paid for by chemotherapy-related morbidity in relapsing cases. The unacceptably high relapse rates spawned attempts to define histopathological criteria predictive of the prognosis. In a retrospective study we found vascular invasion (VI) to be the only statistically significant risk factor of NSGCT I

($P<0.0005$) (Hoeltl *et al.*, 1987b). These retrospective data were validated in a prospective trial based on patient stratification by the presence or absence of vascular invasion. This showed preventive chemotherapy to be effective in patients with a high risk of progression. Both retroperitoneal and visceral tumour spread was reliably prevented in about 95% of cases.

Patients and Methods

Since January 1985 all patients with NSGCT I were stratified prospectively. Details of how vascular invasion was defined have been reported elsewhere (Hoeltl *et al.*, 1987b, 1988). Only obstructing and mural tumour cell thrombi as well as direct invasion of the vascular endothelium by the tumour were considered. Not all investigators were able to distinguish between blood vessel and lymphatic invasion. We would, therefore, agree with most authors that only blood vessel invasion should be considered as vascular invasion, although haema-

Table 1 Risk Factors for NSGCT I from Retrospective Studies

Source	No. pts.	Relapses (%)	pT	Tumour size	Histology	VI	LI
Javadpour	60	17	+	/	E+	+	/
Hoskin	126	28	+	-	E+	+	+
Dewar	28	31	/	/	E+	+	+
Freedman	259	32	-	/	E+(Y-)	+	+
Gelderman	54	20	/	+	-	/	/
Pizzocaro	84	27	+	/	E-	+	/
Dunphy	93	30	/	-	E+	+	/
Thompson	36	33	-	/	-	+	+
Sogani	102	25	/	/	E+	+	/
All	842	27					

+	significant	VI	vascular invasion	/	not investigated	Y	yolk sac tumour
-	not significant	LI	lymphatic invasion	E	embryonal carcinoma		

togenous spread may also originate from lymph node metastases (Liotta *et al.*, 1985).

Patients with NSGCT I were allocated to 2 groups by the presence (VI+) or absence (VI-) of vascular invasion. The VI+ group received 2 chemotherapy courses of bleomycin, etoposide and cisplatin (BEP): bleomycin, 30 mg as a push injection on days 2, 9 and 16; etoposide, 100 mg/m² on days 1 to 5; and cisplatin, 20 mg/m² on days 1 to 5.

The VI- group was subjected to a rigorous surveillance programme. Tumour staging was done by contrast-enhanced mediastinal and retroperitoneal CT with a slice distance of 0.8 cm, chest X-rays in 2 views, and tumour marker assays before surgery as well as on days 5 and 10 post-operatively. Tumour markers were calculated on the basis of the equation below (Lange *et al.*, 1982)

$$T_{1/2} = \frac{-0.693 \times T}{\ln \frac{(\text{conc. } T)}{(\text{conc. } T_0)}}$$

where T is days between 2 titres, conc. T is titre at time 2, conc. T_0 is titre at time 1.

Informed consent was obtained from all patients. Primary tumours were examined grossly using the criteria recommended by the Bonn Testicular Tumour Registry (Thomas, 1982). Histopathological tumour classification was based on the recommendations by Mostofi *et al.* (1973). All histological sections were evaluated by one and the same pathologist (D.K.) with special attention to the predictive factor "vascular invasion". Of the 48 sections evaluated, 6 showed a uniform histological pattern, while 42 were so-called mixed tumours. In both groups, embryonal carcinoma was the most

commonly encountered subtype, with 1 pure embryonal carcinoma in the VI- group and 5 pure embryonal carcinomas in the VI+ group. Overall, embryonal carcinomas (including mixed tumours) were identically distributed in both groups. pT1 disease was more common in the VI- group, while pT2 disease was more often seen in the VI+ group, but the difference was not statistically significant (Table 2).

Results

Since January 1985, 48 patients with clinical stage I NSGCT were admitted to the trial. Mean follow-up time for both groups was 36 months (39 in group A and 33 in group B) (Table 4). Twenty-two patients showed evidence of vascular invasion in the primary tumour. In 21 of them the lesion causing vascular invasion was histologically compatible with embryonal carcinoma (95.4%) (Table 3). Two of the patients in the VI+ group relapsed: 1 of them died of progressive soft tissue and skeletal disease refractory to chemotherapy, the other developed retroperitoneal growing teratoma syndrome with complete remission after surgical excision. The latter was not compatible with a true relapse because the malignant tumour had been successfully eradicated by chemotherapy, so that the correct classification should be "residual mass". A third patient died of small-cell lung cancer without evidence of a testicular tumour at the time of autopsy. Twenty-six patients had no evidence of vascular invasion in the primary tumour (VI-) and undergo a strict surveillance programme. Of these, 1 patient developed pulmonary relapse 3 months following orchiectomy and was cured by

Table 2 Histopathological Patient Data

<i>pT stage*</i>	<i>Group A</i> <i>Vascular invasion negative</i> <i>(VI-)</i> <i>Surveillance</i> <i>No. of patients</i>	<i>Group B</i> <i>Vascular invasion positive</i> <i>(VI+)</i> <i>Adjuvant chemotherapy</i> <i>No. of patients</i>
Total	26	22
pT 1	20	9
pT 2	6	11
pT 3	0	2
<i>Distribution of histological subtypes</i>		
Embryonal carcinoma	21	21
Teratocarcinoma	16	6
Yolk sac	9	6
Choriocarcinoma	6	5
Seminoma	7	7

* TNM classification (UICC, 1987)

chemotherapy. Disease-free survival was 95.8% for both groups (Figs 1-3).

Discussion

The exact definition of vascular invasion is, in fact, a difficult problem for the pathologist. The stringent criteria for the definition as described in previous publications (Hoelzl *et al.*, 1987a, b) were taken as the basis for the correct description of blood vessel

invasion (VI). As vascular and lymphatic invasion cannot be discriminated without misinterpreting artefacts, especially in the capillary network, only true invasion of blood vessels was classified as vascular invasion. We do not know, however, whether other invading histopathological tumour subtypes have the same predictive value as embryonal carcinoma. In our retrospective study, VI by seminomas did not show a significant predictive value for tumour recurrence. There is recent evidence to suggest that embryonal carcinoma invading blood vessels is the most reliable risk factor. The low relapse rate in VI- cases clearly shows that positivity for VI is a reliable parameter predicting relapse.

Table 1 shows all of those reported studies which addressed predictive factors of NSGCT I, particularly the vascular invasion factor (Hoskin *et al.*, 1986; Javadpour, 1986; Dewar *et al.*, 1987; Freedman *et al.*, 1987; Gelderman *et al.*, 1987; Pizzocaro *et al.*, 1987; Dunphy *et al.*, 1988; Thompson *et al.*, 1988). All of them were retrospective. Our trial was based on a prospective design and is the first to stratify a well matched patient population by a predictive factor which is significant for management. Following Liotta's concept of haematogenous tumour spread (Liotta, 1985), the presence of manifest vascular invasion would suggest that the stage of haematogenous spread has been reached. Consequently, locoregional treatment modalities, particularly retroperitoneal lymphadenectomy, can no longer be expected to be curative. Systemic disease calls for systemic treatment. This is the basic tenet of our management concept. In both our retrospective and prospective trials embryonal

Table 3 Tumour Cell Type Invading Blood Vessels in 22 Specimens

Embryonal carcinoma	21
Teratocarcinoma	0
Yolk sac	1
Choriocarcinoma	0
Seminoma	3

Embryonal carcinoma→vascular invasion, in 21/22=95.4%

Table 4 Results

<i>Group A</i> <i>Vascular invasion negative</i> <i>(VI-)</i>	<i>Group B</i> <i>Vascular invasion positive</i> <i>(VI+)</i>
Relapse rate 3.8% (1/26)	Relapse rate 9%* (2/22)
Overall relapse rate: 6.2% (3/48)	
Overall alive with NED: 95.8% (46/48)	
<i>Median follow-up</i>	
39 months (12-56)	33 months (12-54)
NED = 100% (26/26)	NED = 90.9% (20/22)

* 1 mature teratoma

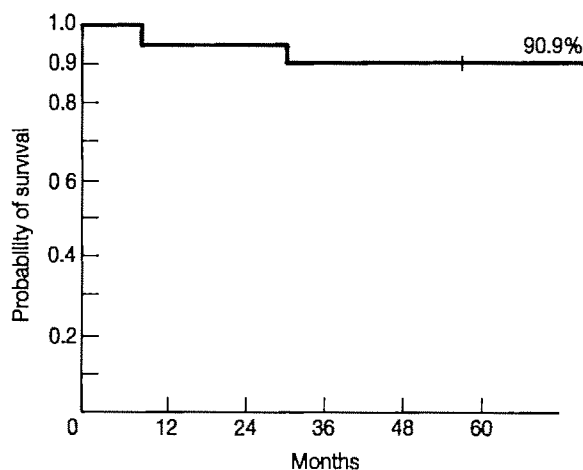


Fig. 1

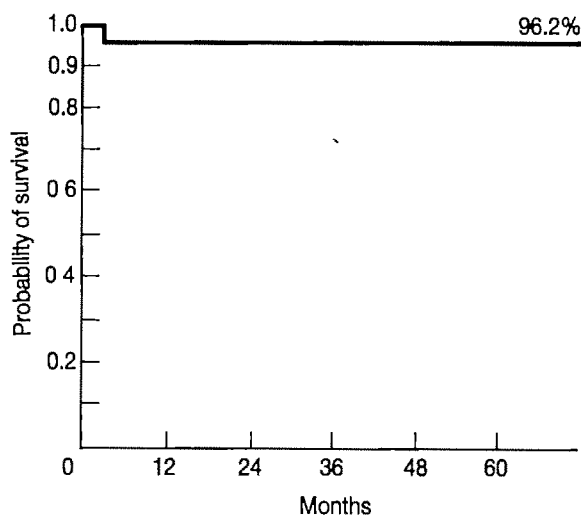


Fig. 2

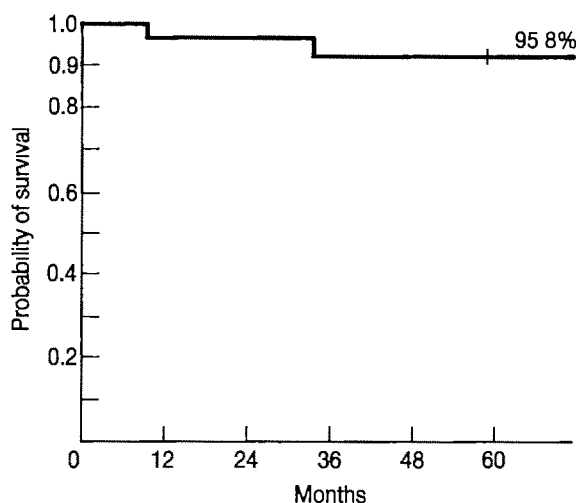


Fig. 3

carcinoma was found to be the most aggressive histological subtype in terms of vascular invasion (Hoeltl *et al.*, 1987b, 1988). Unlike other authors, however, we did not find embryonal carcinoma to be an independent risk factor (Hoskin *et al.*, 1986; Freedman *et al.*, 1987). It was predictive only if associated with vascular invasion. This is also reflected by the distribution of embryonal cancer elements in the tumours seen, which was comparable in the VI- and the VI+ group. Dunphy *et al.* (1988) confirmed this observation.

We believe that, given painstaking clinical and histopathological staging, vascular invasion is a reliable factor for early identification of patients with a high risk of progression and for their adequate treatment. The majority of these patients can definitely be spared progression of their disease. Our goal is to reduce the extent of treatment, while maintaining its efficiency (Hoeltl *et al.*, 1987a). It will be for future studies to show whether microscopic tumour spread can successfully be prevented by chemotherapy regimens of lower toxicity. As the relapse rate in the VI+ group was 9%, it is questionable whether 2 BEP courses are sufficient. Einhorn *et al.* (1989) showed 3 courses of BEP to be as effective in low-volume disseminated disease as 4 courses. In a randomised trial of NSGCT IIB tumours Hartlapp *et al.* (1987) found 2 and 4 courses of PVB to be equally effective. In a prospective randomised trial Williams *et al.* (1987) showed 2 adjuvant courses of platinum-based chemotherapy following retroperitoneal lymph node dissection to be sufficient for preventing relapse in stage II NSGCT. In the observation-only group, by contrast, 49% of patients relapsed, but most of them were cured by chemotherapy administered at the time of recurrence. These 3 reports were the rationale for treating patients with clinical stage I VI+ disease with 2 courses of BEP. This high-risk stage I group probably has disseminated microscopic disease (clinically undetectable tumour) at the time of diagnosis. The actual amount of chemotherapy required for VI+ stage I patients will have to be evaluated in a major prospective randomised trial.

One of the 2 patients classified as relapse suffered from residual mature growing teratoma. It is unclear whether this should be rated as a relapse or rather as a residual benign mass left after chemotherapy. The greatest asset of surveillance strategies is that only patients with established metastatic disease are treated; 70 to 80% of all NSGCT I are cured without adjuvant therapy. But surveillance will work only if patients are reliably co-operative and

follow-ups are rigorously done in one and the same tumour centre by one and the same physician (Sandeman *et al.*, 1979; Peckham *et al.*, 1982; Raghavan *et al.*, 1982). That an occasional recurrent lesion goes unrecognised before it has reached a higher stage is the price to be paid.

Modified (limited) or nerve-sparing retroperitoneal lymphadenectomy, by contrast, is associated with morbidity in terms of ejaculatory loss in 10 to 20% of cases (Jewett and Torbey, 1988; Richie, 1988). As it is diagnostic only, it would no longer appear to be necessary (Hoeltl *et al.*, 1987a). To minimise the disadvantages of a surveillance-only strategy, risk-adapted stratification by VI+ was done. The resultant overall relapse rate for both groups was 6.2% (3/48). This is much lower than reported rates in the literature (Hoskin *et al.*, 1986; Javadpour, 1986; Dewar *et al.*, 1987; Freedman *et al.*, 1987; Gelderman *et al.*, 1987; Pizzocaro *et al.*, 1987; Dunphy *et al.*, 1988; Sogani and Fair, 1988; Thompson *et al.*, 1988). Morbidity attributable to adjuvant chemotherapy is temporary and fully reversible. Fertility is reduced for 1 to 2 years following chemotherapy.

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Non-invasive Management of Impotence with Transcutaneous Nitroglycerin

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Summary—Nitroglycerin plasters were applied to the penis in 10 impotent men and the erectile effect assessed. During laboratory testing all patients achieved an erectile response. Self-administration of nitroglycerin patches restored potency in 4 patients and was preferred to papaverine auto-injection by 3. Headache was a common side effect during initial administration. An attempt to treat impotence with nitroglycerin plaster seems worthwhile before starting extensive investigations or invasive treatment.

The pharmacological management of erectile dysfunction has been based mainly on the intracavernous injection of vasoactive drugs. Auto-injection of smooth muscle relaxant drugs such as papaverine alone or in combination with phentolamine has been used successfully for many years in the treatment of impotence. However, numerous side effects have been reported and many patients (25–50%) have stopped using the auto-injection procedure for various reasons—mainly because of the lack of spontaneity (Kromann-Andersen, unpublished data). Thus a non-invasive therapeutic alternative seems attractive.

The aim of the present study was to evaluate the erectile effect of nitroglycerin patches in impotent men.

Patients and Methods

Following informed consent, 10 impotent men entered the study. The median age was 60 years (range 45–71). The median duration of impotence was 5 years (range 1–10). The patients were consecutively referred for evaluation of erectile dysfunction. Prior to therapy 6 patients were totally impotent and 4 achieved unsustained spontaneous erections. Four patients were already on a successful

papaverine auto-injection regime. Pre-treatment evaluation consisted of history and general physical examination, including perineal neurological tests, penile-brachial blood pressure index measurement and diagnostic intracavernous injection of 30 to 60 mg papaverine. Neither pharmacocavernosometry nor pharmacocavernosography was routinely undertaken. A criterion for the study was a positive erectile response to the diagnostic papaverine test (Table). In 3 patients the bulbocavernosus reflex could not be elicited. One patient had decreased penile blood pressure with a penile-brachial index of 0.63. The main cause of impotence was neurogenic in 3 patients and psychogenic in 1. The remaining 6 patients had a mixed aetiology (psychogenic/arteriogenic in 3, neurogenic/arteriogenic in 2 and neurogenic/psychogenic in 1). The neurogenic aetiology was presumed to be central neurovascular malformation in 1 patient, peripheral autonomic neuropathy due to sigmoid or prostate surgery in 3 and diabetes or alcoholism in 2. No patient was hypertensive, hypotensive or suffering from glaucoma.

We used the 10 mg Transiderm-Nitro plaster (Nitroderm TTS®, Ciba-Geigy) which is used primarily in the treatment of angina pectoris. One 10 mg plaster measures 32 mm × 89 mm and exhibits excellent skin penetration of about 10 mg nitroglycerin/24 h with a constant plasma level

Table Erectile Effect of Intracavernous Papaverine 30–60 mg and Penile Transiderm-Nitro Plaster in 10 Impotent Men

	Full rigidity	Semi-rigidity	Tumescence	No effect
Papaverine test	5	4	1	
Transiderm-Nitro Laboratory test	1	6	3	
Self-administration	4	2	3	1

from 2 to 24 h when applied to the chest. $T\frac{1}{2}$ of the plasma nitroglycerin concentration following removal of the plaster is almost 1 h (Riess *et al.*, 1985). The pharmacokinetics of nitroglycerin with regard to penile patch application are unknown.

The 10 mg Transiderm-Nitro plaster was placed longitudinally on the penile shaft for a 2-h laboratory test. The procedure included penile stasis for 5 min with subsequent objective evaluation of erectile response; blood pressure was not measured. No visual stimulation or penile vibration was used in either the laboratory test or in the preceding papaverine test.

Four plasters were subsequently given to each patient for self-administration once a week. The patients were advised to apply the plaster on the penile shaft 1 to 2 h before intercourse. A questionnaire was completed by the patient after each plaster was used. The erectile response was graded as shown in the Table. For the self-administered plasters full rigidity implied successful intercourse, semi-rigidity a response allowing penetration but not subsequent intercourse, and tumescence only a minor response insufficient for penetration. The patients were prescribed a mild analgesic in case of severe headache: paracetamol to be taken 1 h before applying the plaster.

Results

In the laboratory test all patients achieved an objectively assessed erectile response to Transiderm-Nitro plaster, although this was less pronounced than that following the intracavernous injection of papaverine (Table). The median time from application of the plaster to the response was 30 min. Subjective evaluation of the self-administered plasters showed full rigidity with successful intercourse, orgasm and ejaculation in 4 patients. The median duration of erection in these 4 patients was 30 min (range 15–180). The plasters were worn for a median of 2 h and removed immediately before intercourse on most occasions. The 4 responding patients had intercourse once or twice

a week and were well accustomed to papaverine auto-injection. One had been totally impotent prior to treatment. Three of these patients preferred Transiderm-Nitro to papaverine for the future management of their erectile dysfunction, but 1 preferred papaverine because of the less sustained erection following application of the plaster. The cause of impotence in the responding patients was neurogenic in 1, psychogenic in another, and mixed arteriogenic and psychogenic or neurogenic in the remaining 2.

Two patients reported semi-rigidity insufficient for intercourse. The remaining patients had only minor or no erectile response. Seven patients complained of headache after using the plaster and in 3 cases this was pronounced and discouraged intercourse. Mild analgesics appeared to reduce the severity of the headache. In 1 case the partner reported headache following penetration with the plaster *in situ*. Postural dizziness was not reported.

Discussion

Experience with nitroglycerin in the management of impotence is limited. Bookstein *et al.* (1987) reported improved visualisation of the distal part of the penile arteries following selective pudendal arterial injection of diluted nitroglycerin for vasodilatation pharmacangiography. Nitroglycerin spray to the glans of the penis was used by Wagenknecht (1989) to improve Doppler assessment of vascular impotence. Using ultrasound, Heaton *et al.* (1990) showed a 46% increase in penile arterial diameter 10 min after applying glyceryltrinitrate paste to the shaft of the penis. *In vitro* glyceryltrinitrate was shown to relax the penile cavernous trabecular smooth muscles in impotent men (Heaton, 1989). Other reports have indicated that impotent patients respond to nitroglycerin taken sublingually or applied to the penis (Mudd, 1977; Talley and Crawley, 1985). In a placebo-controlled study Owen *et al.* (1989) observed an increase in penile circumference with the strain

gauge technique following visual stimulation and application of nitroglycerin paste.

In the present study, Transiderm-Nitro plaster produced an objective erectile response in all patients during laboratory tests and potency was restored in 4 patients following self-administration. This non-invasive treatment was preferred to papaverine auto-injection by 3 of the 4 responding patients. Headache was partially relieved by mild analgesics. The repeated application of nitroglycerin plaster may reduce this side effect (Riess *et al.*, 1985). The present study was neither double-blind nor placebo-controlled. It is probably difficult to conduct a valid blind, placebo-controlled study because of the high incidence of headache. Furthermore, some placebo effect from the use of nitroglycerin plaster is acceptable if this treatment restores potency even in patients with psychogenic impotence.

A randomised placebo-controlled study of transcutaneous nitroglycerin therapy in 26 impotent patients was reported by Claes and Baert (1989). They observed an almost identical complete response rate, with a return to satisfactory sexual function in 46% of their patients and some erectile improvement in a further 35%. The placebo patches restored potency in only 1/26 patients in this study. Headache was common initially but only 15% were excluded from treatment because of persistent headache. The clinical effect of Nitroderm TTS 10 mg was further confirmed by Negelev (1990), who reported, on the basis of a 1-year clinical study, improved erection in patients with organic as well as psychogenic impotence. The results were best in elderly patients, but in younger patients, most of whom had diabetes, this agent was of no use. However, no detailed data were presented.

We believe that the effect of topical nitroglycerin on erectile function deserves further study and that this agent should be used to treat impotence before embarking on further assessment and invasive treatment. It is possible that many men with subclinical erectile dysfunction might benefit from

this non-invasive and inexpensive treatment. Precautions should be taken in patients with known hypersensitivity to nitroglycerin, with circulatory failure associated with hypotension and in patients with elevated intracranial pressure or glaucoma. Alcohol and other vasodilators may potentiate the hypotensive effect of topical nitroglycerin.

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PAEDIATRIC UROLOGY

Gastrocystoplasty in Children

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Summary—We report our experience of gastrocystoplasty in 8 children (mean age 10.1 years) with compromised renal function (mean creatinine 186 mmol/l, mean glomerular filtration rate 39 ml/min/1.73 m²).

Current follow-up ranges from 11 to 35 months (mean 21). The physiological outcome of the procedure has been excellent, with improved biochemical and urodynamic parameters in all cases. Six patients are off H₂-receptor blockers and are asymptomatic. In 2 children we have encountered significant symptoms related to acid secretion in the bladder.

Detailed investigations suggest that the excess aciduria is related to the size of the gastric patch in 1 patient. The second child underwent renal transplantation 5 months after gastrocystoplasty and it is postulated that his immunosuppressive regimen (which includes prednisolone) may be responsible for the increased acid secretion.

It is concluded that gastrocystoplasty is a very satisfactory alternative to intestinal segment bladder enhancement in children with compromised renal function, but the size of the gastric patch is critical in determining the resultant acid secretion. Post-transplantation immunosuppressive therapy may increase acid production from the gastric patch; since the children most suitable for gastrocystoplasty are also those likely to require transplantation, this aspect requires further study.

Gastrocystoplasty has been reported to be a useful alternative to intestinal segment bladder enhancement in patients with compromised renal function (Adams *et al.*, 1988). The advantages of using the stomach include protection against hyperchloraemic acidosis (due to a net excretion of chloride), reduced mucus production and decreased urine infection rates (Leong, 1978; Adams *et al.*, 1988; Kennedy *et al.*, 1988). The procedure has been used in children without any reported complications of excess aciduria (Adams *et al.*, 1988).

We report our experience with this technique in 8 children with reduced renal function, 2 of whom have had significant symptoms related to acid secretion from the gastrocystoplasty.

Patients and Methods

Since 1988, 7 boys and 1 girl have undergone bladder augmentation with a segment of stomach.

The children were aged from 14 months to 16 years (mean age 10.1 years) and the primary causes of lower tract dysfunction included posterior urethral valves (5 patients), bladder exstrophy (1) and urethral diverticulum (1). The only girl in the series had a contracted, hypocompliant bladder as a result of radiotherapy for uterovaginal malignancy in infancy.

The indication for using the stomach rather than intestine for bladder enhancement was the presence of compromised renal function and a tendency to acidosis in all cases. The mean plasma creatinine was 186 mmol/l (range 60–391) and the mean pre-operative glomerular filtration rate (GFR) was 39 ml/min/1.73 m² (range 12–75). Total plasma CO₂ levels ranged from 17 to 25 mmol/l (mean 20.7) and 3 children were receiving oral bicarbonate supplements.

Pre-operative urodynamic studies showed a reduced bladder capacity (mean 106 ml) and high end-fill pressures (mean 54 cm H₂O) in all patients.

A diamond-shaped segment of the body of the stomach based on a pedicle from the left gastropiloric artery was used to enhance the bladder in

all cases. The short axis measured along the greater curvature ranged from 6 to 10 cm and the estimated surface area of the segment ranged from 40 to 80 cm² (mean surface area 54 cm²). Three children had continent catheterisable conduits (Mitrofanoff (1980) procedure) created at the time of the gastrocystoplasty (appendico-vesicostomy 2, uretero-vesicostomy 1).

Intravenous H₂-receptor blockers (cimetidine) were commenced intra-operatively in all patients and continued during the post-operative period until spontaneous voiding or clean intermittent catheterisation was resumed.

All patients were reviewed regularly following discharge from hospital. Blood electrolytes, creatinine, GFR and acid-base status were monitored, and 24-h urine collections were made for pH estimation, titratable acidity and urinary acid output. Regular urine cultures were also obtained. Six patients had at least 1 fasting gastrin level measured and repeat urodynamic studies and cystoscopy were also performed.

Results

No technical difficulties were encountered and there were no immediate post-operative problems. There have been no complications related to the creation of a Mitrofanoff conduit in the presence of a gastrocystoplasty, even when the appendix was used.

The mean follow-up is currently 21 months (range 11–35) and in all patients the physiological outcome has been very satisfactory. Blood acid-base status has improved despite persisting renal compromise. Fasting plasma gastrin levels are within the normal range in 5/6 patients (Table 1). One child has a measured fasting gastrin of 58 pmol/l (normal range <40) but this is not considered to be clinically significant.

Table 1 Effect of Gastrocystoplasty (GCP) on Blood Biochemistry

	Before GCP	After GCP	Normal range
Creatinine (mmol/l)	60–391	30*–333	30–102
(mean)	(186)	(151*)	
Chloride (mmol/l)	100–109	100–112	98–106
(mean)	(104)	(105)	
Total CO ₂ (mmol/l)	17–25	22–28	20–26
(mean)	(20.7)	(25.2)	
Gastrin (pmol/l)	–	7–58	<40
(mean)		(28)	

* Includes 1 patient following renal transplantation.

Post-operative urodynamic studies have shown a marked improvement in bladder capacity (mean capacity 324 ml) and compliance (mean end-fill pressure 25 cm H₂O) in all cases. On cystoscopy there is no evidence of gross mucosal change or ulceration in any gastric patch or bladder remnant. The junctions between gastric and transitional epithelium are well healed and remain sharply demarcated.

In 6 children H₂-receptor blockers were discontinued before discharge from hospital or shortly afterwards, and all have remained asymptomatic. Their urinary pH and acid output levels are shown in Table 2. However, in 2 patients we have encountered significant symptoms related to acid secretion within the bladder. These patients are described in more detail below.

Case Reports

Case 1. A 9-year-old boy with a primary diagnosis of posterior urethral valves underwent gastrocystoplasty in July 1988. The procedure was uncomplicated and he was discharged, voiding spontaneously and off cimetidine, 16 days following operation. He was readmitted 1 week later with severe dysuria, frank haematuria and clot retention. Suprapubic catheter drainage was instituted but the bleeding continued until oral cimetidine was recommenced. After 1 week his symptoms abated and he was discharged on oral cimetidine therapy, but over the ensuing 6 months he continued to complain of intermittent pain and haematuria. Oral bicarbonate was added to his therapy without success and a subsequent change from cimetidine to ranitidine also failed to control his symptoms.

One year following gastrocystoplasty he was admitted for further investigation. Blood chloride, total CO₂ and gastrin levels were normal, but his urinary titratable acid and acid output levels were higher than those seen in the asymptomatic patients (Table 2). A 24-h intravesical pH profile was obtained (using an oesophageal pH probe inserted suprapubically) which showed that despite intermittent voided urine pH levels of 4.4 to 6.7, the intravesical pH was ≤3 for more than two-thirds of the day (Fig. 1A). He was therefore commenced on oral omeprazole, a substituted benzimidazole which blocks gastric acid secretion at the level of the proton pump in the apical membrane of the parietal cell (Wolfe and Soll, 1988). After 48 h of omeprazole therapy a repeat 24-h intravesical pH profile showed a significant increase in intravesical pH with values ≥5 for >90% of the day (Fig. 1B). He was discharged on oral omeprazole 40 mg/day.

Although this treatment abolished the haematuria and diminished his pain, he continued to complain of intermittent dysuria throughout the next 12 months. Urine cultures were sterile but repeat 24-h urine collec-

Table 2 Urine Biochemistry following Gastrocystoplasty (GCP)

	<i>Voided urine pH</i>	<i>Titratable acidity (mmol/l)</i>	<i>Acid output (mmol/day)</i>
Asymptomatic patients (mean of 6)	4.5–6.0	3.4–6.3 (5.2)	5.1–31 (19)
Case 1 (1 year after GCP)	4.4–6.7	28	75.6
Case 1 (on omeprazole)	5.5–6.7	11.7	30.1
Case 2 (1 year after GCP, 5/12 after transplant)	2.0–4.5	6.0	9.8

tions showed that despite omeprazole, urinary acid excretion remained higher than that seen in the asymptomatic patients (Table 2). Cystoscopy showed no evidence of mucosal abnormalities, but it was decided to attempt obliteration of part of the acid-secreting mucosa. He underwent laser therapy to the gastric patch in May 1991, but to date has had no significant symptomatic improvement. It is likely that he will require surgical reduction of the area of acid-secreting mucosa within his bladder enhancement.

Case 2. A 14-month-old boy with a primary diagnosis of posterior urethral valves underwent gastrocystoplasty in

January 1990. His pre-operative renal function was severely compromised (creatinine 352 mmol/l, GFR 12 ml/min/1.73 m²); despite oral bicarbonate supplements he was persistently acidotic (total plasma CO₂ = 19 mmol/l) and was listed for renal transplantation.

The bladder was augmented with a wedge of stomach and a Mitrofanoff conduit was created from the stump of the left ureter after removal of a completely non-functioning left kidney. He was maintained on intravenous cimetidine post-operatively. One week following operation he developed frank haematuria and was found to have a *Pseudomonas* urinary infection. The haematuria resolved with antibiotic therapy and the cimetidine was

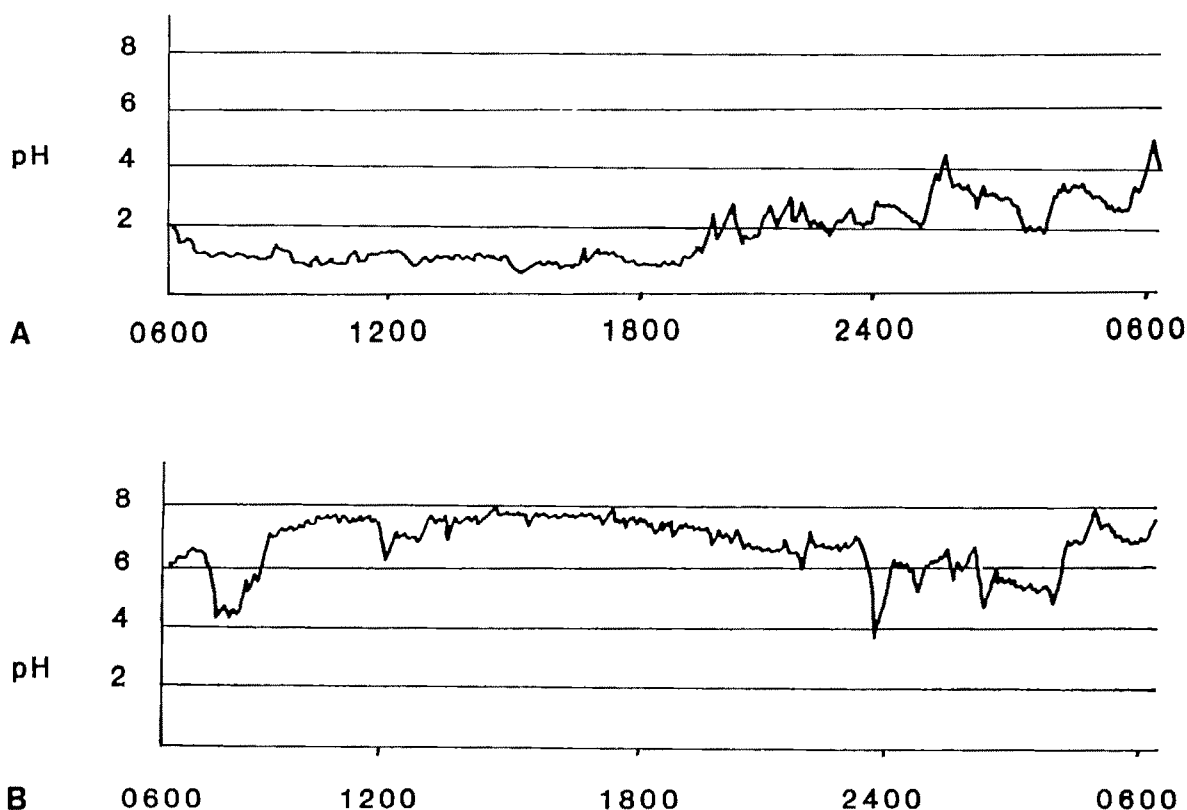


Fig. 1 24-h intravesical pH profile in Case 1 (A) 1 year after gastrocystoplasty and (B) after treatment with omeprazole.

discontinued prior to discharge on the 22nd post-operative day. Unfortunately, owing to an administrative error, he was maintained on his bicarbonate supplements and was readmitted 1 week later with severe systemic alkalosis. This resolved rapidly after cessation of the bicarbonate and re-institution of cimetidine therapy. After stabilisation of his biochemical status the cimetidine was discontinued and he was again discharged.

He remained asymptomatic until he underwent renal transplantation in August 1990. He was briefly recommenced on H_2 -receptor blockers (ranitidine) in the immediate post-transplant period. Although the transplant was successful, he began to experience intermittent dysuria and penile pain when the ranitidine was stopped, and it has been necessary to maintain this treatment. Urine cultures were sterile and blood and urine biochemistry was satisfactory except for occasional urine pH levels of 2. Daily urinary titratable acid levels and acid outputs were within the range seen in the asymptomatic patients (Table 2).

It was found that there was a chronological association between the emptying of residual urine via the Mitrofanoff and the occurrence of his symptoms. It was also noted that he was receiving daily prednisolone therapy as part of his post-transplantation immunosuppressive regimen. He was commenced on topical bicarbonate bladder washouts (via the Mitrofanoff) as required and is currently asymptomatic.

Discussion

The concept of using a segment of stomach as a bladder substitute was first introduced by Sinaiko in 1956. The technique was pioneered clinically in adults by Leong (1978, 1988), who used an antral pouch to replace or augment the bladder in patients with carcinoma or tuberculous disease. Mitchell and colleagues have explored the use of a segment of the body of the stomach for bladder reconstruction in an increasing number of children and have not experienced any difficulties related to acid secretion in the bladder (Adams *et al.*, 1988).

The reported benefits of gastrocystoplasty over intestinal segment augmentation include reduced chloride reabsorption and net chloride excretion by the gastric mucosa, decreased mucus production, decreased urinary infection in the presence of acid urine, ease of ureteric reimplantation and good compliance due to the thick muscular layers of the gastric wall (Leong, 1978; Adams *et al.*, 1988; Kennedy *et al.*, 1988; Rink, 1988; Nurse and Mundy, 1989). Gastrocystoplasty has been advocated in patients with compromised renal function and acidosis, since the protection against hyperchloraemic acidosis is particularly advantageous in

this group and may even be therapeutic (Adams *et al.*, 1988).

Our experience with this procedure has for the most part corroborated that of others, in that we have found it to be technically straightforward and physiologically satisfactory even in small children. The gastric wall has easily accommodated ureteric and Mitrofanoff reimplantation and the urodynamic consequences have been satisfactory. The metabolic results of the procedure in our group of severely compromised patients have also been highly beneficial. Gastrin levels have not been found to rise in patients with antral gastrocystoplasties (Lim *et al.*, 1983) and we have not found any significant elevations in any of our patients.

Some concern over the potential for long-term mucosal changes has been raised by Klee *et al.* (1990), who found a significant incidence of papilloma formation and squamous epithelial hyperplasia in the bladders of rats which had undergone gastrocystoplasty more than 1 year previously. We have seen no evidence of mucosal changes on cystoscopic evaluation, even in the children with symptoms of excess aciduria, but long-term follow-up in this respect is clearly necessary. It must not be forgotten that there is also a potential for mucosal change after intestinal segment bladder enhancement (Mansson and Willem, 1988; Nurse and Mundy, 1989).

The acid-related symptoms experienced by 2 of our patients have not been encountered in other studies (Adams *et al.*, 1988; Mitchell, 1988). Both children displayed recurrent symptoms of acid-induced bladder irritation, despite the absence of visible inflammation or ulceration. Although the symptoms have been controlled by topical antacid therapy in 1 child, the other has required complex manipulations of acid-blocking drugs, none of which has been successful. It is worth noting that the administration of oral bicarbonate (which has been advocated by others (Leong, 1988)) was not helpful. In retrospect this is not surprising, since oral bicarbonate increases the intragastric pH and thus stimulates gastrin production, which in turn stimulates increased acid production from parietal cells (Wolfe and Soll, 1988). In patients with gastric-body enhancements this will result in an increase in bladder acid rather than a decrease. In contrast, topical intravesical bicarbonate neutralises the acid and produces the desired effect.

Our search for possible causes of excess aciduria in our symptomatic patients has revealed some considerations which have not been emphasised previously. Firstly, the intermittent measurement

of voided urine pH may not be a good representation of changes in intravesical pH at mucosal level. The presence of buffers in renal urine can mask high levels of intravesical acid secretion, which are of greatest significance when the bladder is empty. In the child with a gastrocystoplasty, a small volume of residual post-micturition urine may be beneficial, in contrast to the situation with intestinal bladder enhancement, where residual urine may lead to mucus precipitation and stone formation.

The second consideration is the size of the gastric patch which is used for augmentation. In children, the distribution of antral mucosa is very variable, and is maximal along the lesser curve of the stomach. Consequently it is inevitable that most, if not all, of the mucosa in a wedge gastrocystoplasty will be parietal rather than antral. The size of the patch is therefore a major factor in determining the level of intravesical acid production. We have found a positive correlation between the estimated surface area of the gastric patch and the urinary acid levels in our patients ($r=0.96$), but the number of patients is too small for this to be significant. It is noteworthy that the relative area of the patch (expressed as a proportion of body surface area) was greatest in our 2 symptomatic patients (Table 3).

A further consideration is the potential effect of post-transplant immunosuppressive therapy on gastric acid secretion. Steroids are known to potentiate gastric acid production and currently form part of most maintenance immunosuppression regimens in addition to being widely used in the treatment of rejection. It is possible that transient rises in circulating steroid levels occurring at the time of peak drug absorption may be sufficient to stimulate excess aciduria and cause symptoms, particularly when the bladder is empty. To our knowledge, this is the first report of the post-

transplant course of a child with a gastrocystoplasty. Since the patients most likely to be selected for gastrocystoplasty are also those likely to require renal transplantation, this is an area which warrants further investigation.

It is concluded that gastrocystoplasty offers a satisfactory alternative to intestinal segment bladder enhancement in children with compromised renal function. A patch surface area $\leq 0.5\%$ of body surface area is desirable, and the effects of post-transplant steroid therapy must be borne in mind. Long-term follow-up for mucosal changes within the augmented bladder is also necessary.

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Table 3 Relationship between Surface Area of Gastric Segment and 24-h Urinary Titratable Acidity

	Surface area of gastric segment		Titratable acidity (mmol/l)
	cm ²	% body surface area	
Asymptomatic group (mean of 6)	40-56 (48.5)	0.33-0.5 (0.41)	3.4-6.3 (5.2)
Case 1 (symptomatic)	80	0.64	28.0
Case 2 (symptomatic)	50	1.2	6.0

Case Reports

A Male Pseudohermaphrodite with Noonan's Syndrome

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Noonan's syndrome was first described in 1963. It is a heterogeneous malformation syndrome which affects both sexes and is associated with characteristic facies, short stature, cardiac defects and various other abnormalities. It is not, however, associated with chromosomal defects. Urological features may include cryptorchidism, delayed puberty and micropenis (Lyons-Jones, 1988). Fertility is variable. Rotational errors, ureteric duplication and hydronephrosis have been noted on urography (Redman, 1973). We report a male with Noonan's syndrome and occult pseudohermaphroditism, presenting as an acute abdominal emergency.

Case Report

A 29-year-old male with Noonan's syndrome presented with an 18-h history of continuous pain in the right iliac fossa. This was not associated with nausea, gastrointestinal upset or urinary symptoms. A number of similar episodes had occurred over the past 5 years, though none

had been so severe. Bilateral inguinal explorations had been undertaken 18 and 13 years previously and had not revealed testes. Examination revealed a short, bewigged, caucasian male with hypertelorism and downward slanting palpebral fissures. He was pyrexial with a temperature of 37.6°C, and tachycardic. The cardiorespiratory systems were normal. Abdominal examination revealed bilateral double inguinal incisions and tenderness with peritonism in the right iliac fossa, without palpable masses. Rectal examination revealed tenderness anteriorly and to the right. Glandular hypospadias, a small penis and an empty scrotum were noted. Investigations revealed a polymorphonuclear leucocytosis of $13 \times 10^9/l$ and a gram-negative urinary tract infection. In spite of this last finding, the clinical diagnosis of appendicitis was made, but at operation the appendix was normal. Two small (2 cm) testes were found on the posterior abdominal wall above the internal rings. One was biopsied. A bilobed structure, the 2 lobes of which were shaped like the horns of a bicornuate uterus, was present, projecting upwards from the base of the bladder. The right lobe was inflamed and swollen to approximately 6×2 cm. Aspiration revealed a small volume of pus. No structures resembling seminal vesicles or vasa deferentia were seen. Post-operatively the patient improved on amoxycillin, to which both the urinary coliform and the gram-negative bacillus cultured from the aspirated pus were sensitive. A magnetic resonance imaging (MRI) scan was subsequently performed (Fig.). The testicular biopsy demonstrated tubular atrophy. Chromosomal studies were normal.

Comment

Male pseudohermaphroditism results from a failure of suppression of paramesonephric (Müllerian)

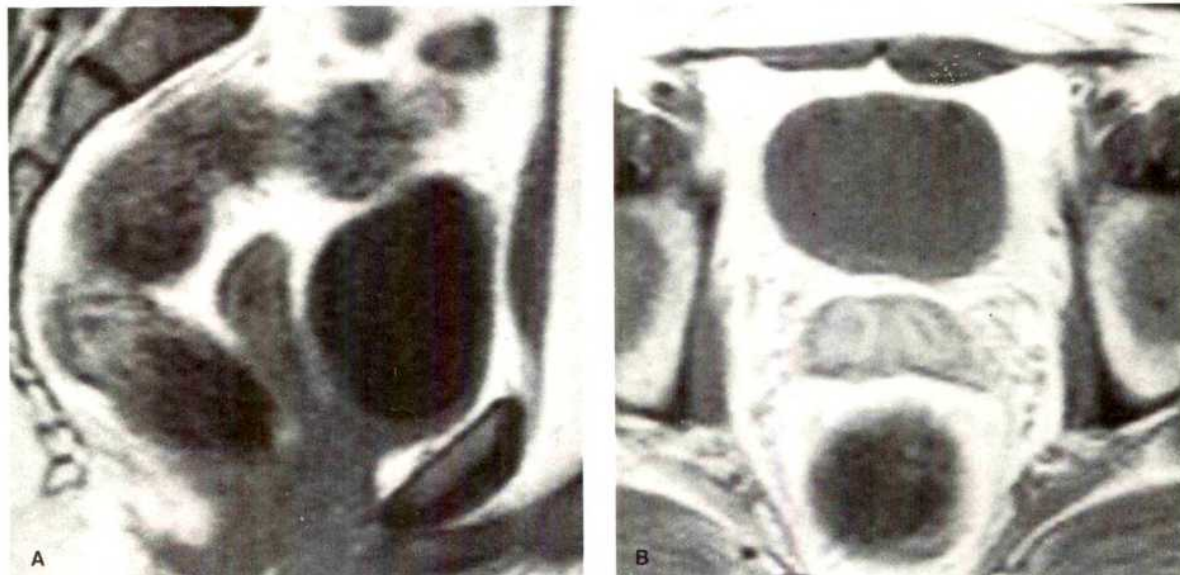


Fig. Magnetic resonance images of patient's pelvis in sagittal (A) and transverse (B) planes. The bilobed uterus lies between the bladder anteriorly and the rectum posteriorly.

structures by fetal androgens, with a degree of hypospadias and the variable coexistence of Müllerian and mesonephric (Wolffian) derived internal genitalia. Such is the case in the adrenogenital syndrome and the testicular feminisation syndrome (Hamilton and Mossman, 1972). It has not been described in relation to Noonan's syndrome.

Our patient presented with the clinical picture of acute appendicitis but the true diagnosis of an infected cornu of a rudimentary uterus was not apparent prior to operation, despite the presence of a urinary tract infection.

It is concluded that similar presentations may be managed conservatively, obtaining accurate images by computed tomography or MRI to define the anatomical abnormality, prior to treatment with antibiotics.

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Bilateral Hydronephrosis Secondary to Breast Carcinoma Metastasising to the Bladder

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Case Report

A 79-year-old lady presented with a short history of frequency and nocturia without dysuria or haematuria. Urine cytology showed malignant cells and an intravenous urogram revealed normal-sized kidneys with prompt excretion on the left filling a dilated ureter down to the bladder. On the right there was delayed excretion followed by an increasingly dense nephrogram. There was a large filling defect in the bladder vault (Fig.), suggesting bladder carcinoma causing ureteric obstruction. At cystoscopy a large tumour was seen in the bladder vault and biopsies were taken. Only the right ureteric orifice could be found and a stent was inserted. The patient's clinical condition subsequently deteriorated and she died from renal failure.

Histology of the mass showed extensive infiltration of bladder muscle by breast carcinoma. Mastectomies had been carried out 30 and 6 years previously. There was evidence of local recurrence on the left.

This lady died of renal failure secondary to ureteric obstruction caused by direct bladder invasion by metastatic breast carcinoma.

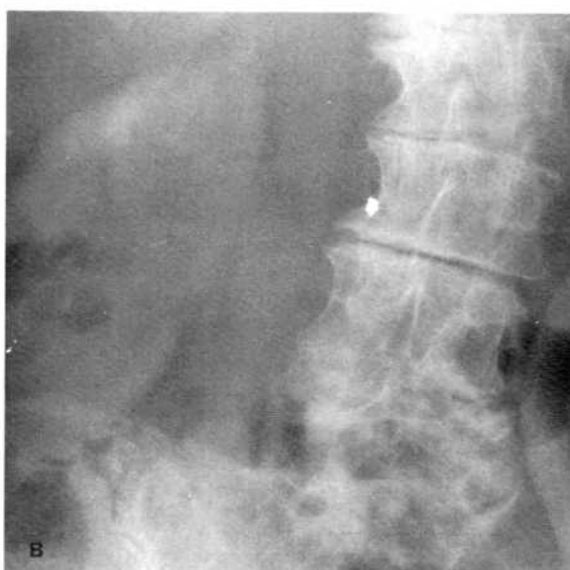
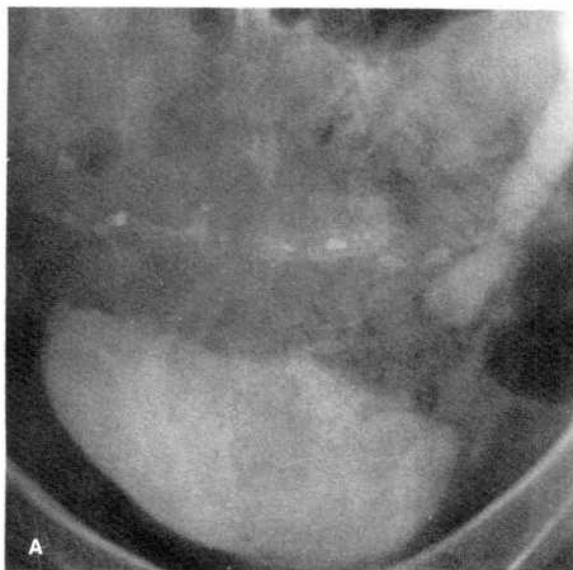


Fig. Intravenous urogram films taken 5 h after injection. The left ureter is dilated by an obstruction at the bladder (A) and the right ureter is not shown but there is a dense nephrogram (B). The filling defect in the bladder is present.

Comment

Symptomatic and life-threatening metastatic involvement of the ureters is uncommon. Prostate and cervical cancer obstruct by direct spread but colonic and breast cancers are the most common otherwise (Richie *et al.*, 1979). The usual mechanism of obstruction is by malignant retroperitoneal fibrosis (Grabstald and Kaufman, 1969). There is only one other case in the literature caused by direct involvement of the bladder (Silverstein *et al.*, 1987). Early treatment with either local or systemic measures increases the chances of successful management of the renal failure.

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Seminal Vesicle Cyst, Renal Agenesis and Epididymitis in a 50-year-old Patient

M. J. LYNCH and G. M. FLANNIGAN, *Department of Urology, Royal Infirmary, Bradford*

Case Report

A 50-year-old man presented in 1989 with left epididymitis. His infection settled on antibiotics. Mid-stream urine culture produced a significant growth of coliforms. Intravenous urography showed a hypertrophied right kidney with no obvious left kidney. Ultrasound showed a thick-walled cystic structure behind the bladder on the left side and no left kidney was found. Computed tomography (Fig.) suggested a seminal vesicle cyst. Although the patient remained asymptomatic, urine culture persistently grew coliforms. The cyst was excised by the transvesical approach (Palmer, 1986).

Comment

Seminal vesicle cysts associated with renal agenesis

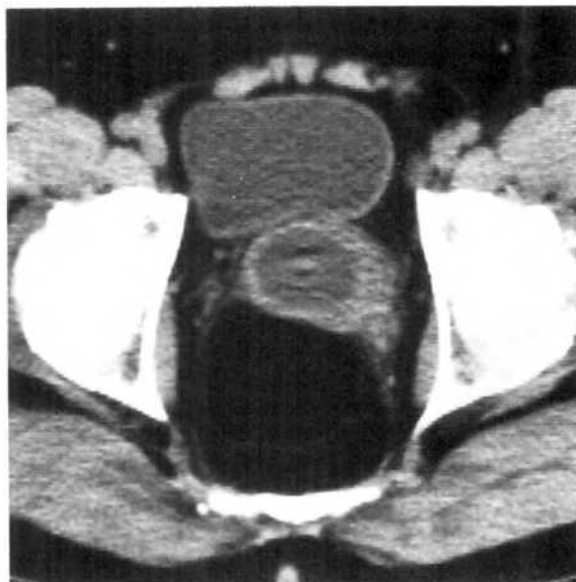


Fig. CT scan of pelvis showing seminal vesicle cyst.

are uncommon and usually present with pain on intercourse, bladder irritation or epididymitis in the years of maximal sexual activity (Heaney *et al.*, 1987). This is the second patient presenting with epididymitis seen at this hospital in the last year, the other being a 28-year-old man.

Our suspicion was initially aroused by the absence of a kidney on the urogram ipsilateral to the epididymitis, the diagnosis being made by ultrasonography.

Excision of the cyst was difficult and much of the dissection was more easily and safely performed by an extravesical extraperitoneal approach.

Although this is not the oldest patient to be reported, others have been discovered incidentally (Kaneti *et al.*, 1988). We report this patient to emphasise that seminal vesicle cysts associated with renal agenesis may present late in life.

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Vesicosigmoid Fistula as an Incidental Finding Accompanying Bladder Cancer

N. E. STAVROPOULOS, D. S. KONTOGIANNIS, J. S. STAVRIDADIS and K. J. GOSSIOS, *Department of Urology, University of Ioannina, and Department of Computed Tomography, General Hospital "Hatjikosta", Ioannina, Greece*

Fistulas between the intestinal tract and the urinary bladder are uncommon and are usually secondary to intestinal disease (Moisey and Williams, 1972).

Case Report

A 72-year-old male with an indwelling catheter was referred with an 8-month history of voiding difficulties and episodes of painless haematuria.

Physical examination revealed a frail old man with a tender mass in the lower abdomen. The urine was infected with *Escherichia coli*. Laboratory investigations revealed the following: WBC $14.7 \times 10^9/l$; RBC $3.96 \times 10^{12}/l$; Hb 12.8 g/dl; Hct 38.8%; BUN 80 mg/dl; creatinine 2.6 mg/dl; uric acid 11.3 mg/dl. Chest X-ray was normal. Bilateral obstruction at the vesicoureteric junctions and poor delineation of the urinary bladder on the intravenous urogram led us to perform an abdominal CT scan (Figs 1 and 2). No distant metastases were noted. Cystoscopy and biopsy demonstrated a large G3 transitional cell carcinoma of the bladder. The patient refused treatment.

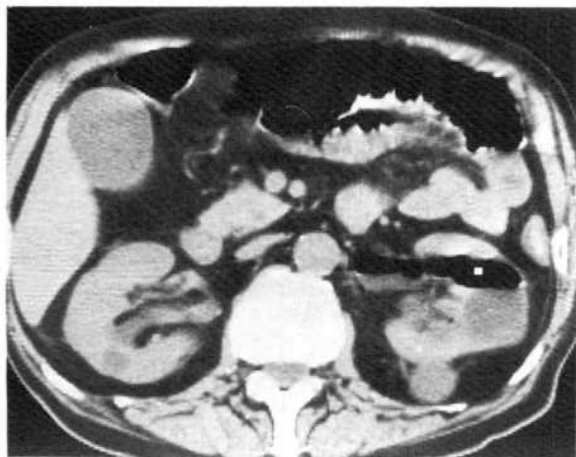


Fig. 1 CT scan after instillation of contrast into the bladder, showing extravasation of contrast into the sigmoid colon, and gas in the bladder and left ureter.

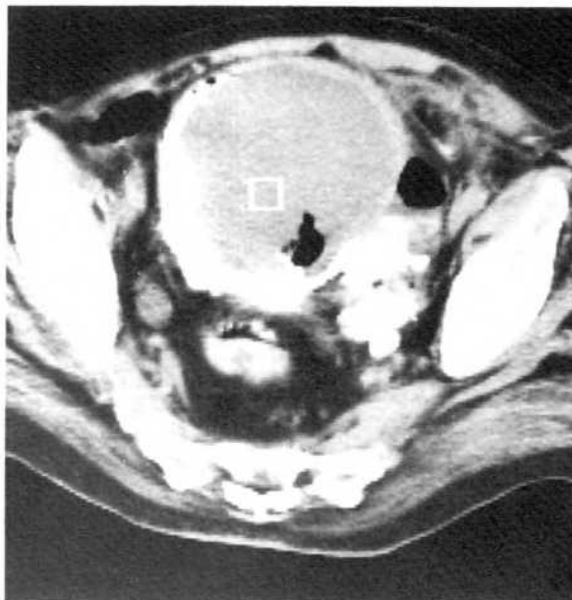


Fig. 2 CT scan showing gas in the left ureter and collecting system of the left kidney.

Comment

The overall incidence of urological causes among 867 cases of enterovesical fistula presented in 23 series is 1.9% and among these bladder cancer is rare (Vidal Sans *et al.*, 1986).

While pneumaturia and faecaluria are present in a high percentage of patients (56%) and are regarded as symptoms diagnostic of enterovesical fistula, haematuria was the predominant symptom in our patient.

The retrograde cystogram can delineate the fistulous tract in up to 67% of patients (Vidal Sans *et al.*, 1986) and, if performed by computed tomography in cases of bladder cancer, the extent of the underlying disease can be evaluated at the same time.

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The Persistent Indwelling Catheter

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Self-retaining balloon urethral catheters can occasionally be difficult to deflate and remove. Various solutions to this problem have been suggested, including hyperinflating the balloon with water or ether, cutting off the inflating arm of the catheter, introducing a wire stylet and puncturing the balloon transrectally under antibiotic cover. These methods have been superseded by transabdominal ultrasound-guided puncture of the balloon.

Often no cause can be found for the trouble but occasionally there is some obstruction to the egress of the fluid from the balloon; this is usually caused by a small foreign body—even a tiny fragment of glass from the ampoule containing the water. Crimping or concertina formation of the deflated balloon makes it a traumatic experience for the patient and is even worse when a plastic (transparent) catheter has been used, since the material of which the balloon is composed is less pliable than latex or silicone. The deflated catheter may be gently coaxed out with some degree of sharp traction when the balloon reaches the meatus, thereby aggravating the patient and damaging the meatus. Alternatively, the deflated catheter may be pre-lubricated by introducing lignocaine gel through the main channel of the catheter in order to coat the crimped up balloon and then waiting a few minutes before removing the catheter.

We have recently experienced a new problem when removing the catheter. It was seen that all

but the last 2 to 3 ml of fluid from the balloon can be removed because the elastic recoil in the balloon closes the orifice of the inflating channel (Fig.) before all of the fluid has been removed; in addition, the volume of fluid in the balloon is not sufficient for it to be located and punctured using ultrasound. Other urologists may have had a similar experience with 2-way or 3-way plastic transparent catheters used after transurethral surgery. The product has not been named but the manufacturers are being informed of this problem.

Acknowledgements

The author thanks the staff nurses on the surgical wards and Dr Barnardo for their help in collecting the catheter tips.

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Vesico-coccygeal Fistula Revealing Pelvic Malakoplakia

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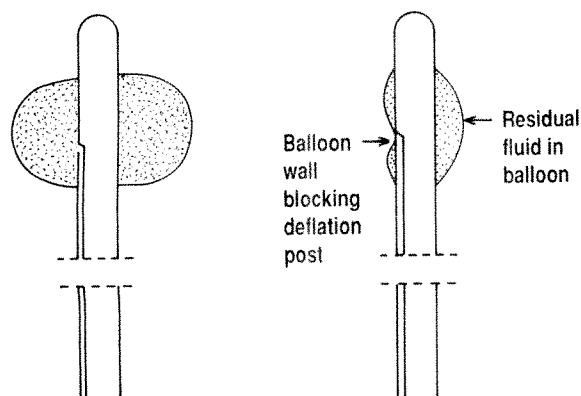
Case Report

A 62-year-old man with a previous history of diabetes mellitus, sigmoid diverticulitis and chronic liver insufficiency presented in September 1987 with a perianal abscess. Drainage of the abscess was followed by urinary leakage. Intravenous urography failed to visualise the fistula but the CT scan showed an intravesical mass (Fig. 1) and the diagnosis of bladder malakoplakia was made after transurethral resection. Rectosigmoidoscopy performed because of sigmoid diverticulitis showed rectal malakoplakia.

The patient denied recurrent urinary tract infections and the cultures were only occasionally positive for *Escherichia coli*. Nevertheless, antibiotic treatment was started with ofloxacin and trimethoprim-sulphamethoxazole. The fistula healed and the patient did well until February 1989, when both cystoscopy and CT scan showed regression of the disease (Fig. 2).

In September 1989 the patient was readmitted with a recurrence of the urinary leakage from the coccygeal fistula. CT scan, barium enema and fistulography revealed a vesico-coccygeal and a recto-pararectal fistula (Fig. 3).

Total cystectomy with Bricker diversion was carried out, recovery was uneventful and the patient was discharged under medical treatment for diverticulitis.



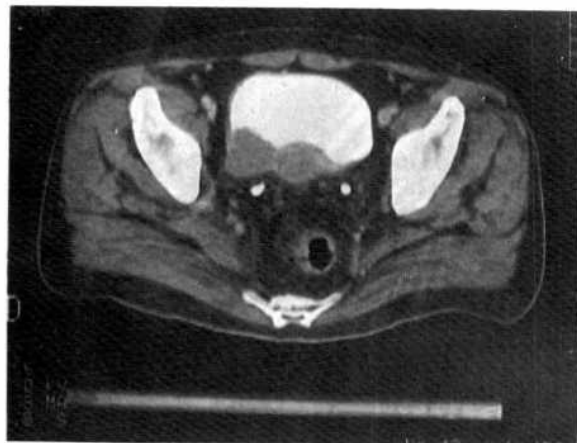


Fig. 1 CT scan showing mass protruding into the bladder and extending to the right pelvic wall.



Fig. 3 Fistulography; contrast dye injected from the skin reaches the bladder.

Comment

Malakoplakia is a non-specific granulomatous disease that affects many body tissues but most frequently the genitourinary tract. The bladder is involved in almost 60% of cases, followed by renal parenchyma (16%), renal pelvis and ureter (10%), urethra (2%), prostate (30 cases reported in the literature) and testis (Long and Althausen, 1989; Sujka *et al.*, 1989).

Unlike upper tract disease, malakoplakia of the lower urinary tract is generally considered a benign, self-limiting process, although extensive pelvic spread has occasionally been observed. Of the 3

patients reported in the literature as suffering from pelvic malakoplakia, 2 were cured by conservative therapy but 1 requested total pelvic exenteration (Abdou *et al.*, 1977; Matthews *et al.*, 1986; Long and Althausen, 1989).

The clinical presentation of bladder malakoplakia is dominated by non-specific irritative symptoms and haematuria. This seems to be the first reported case of a vesico-coccygeal fistula revealing the disease.



Fig. 2 CT scan showing reduction in extent of disease inside the bladder but persistence of malakoplakia involving the right pelvic wall.

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Spontaneous Rupture of the Bladder in Interstitial Cystitis

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Pathology, Maternity Hospital, Bristol*

Rupture of the normal bladder is rare, especially in the absence of trauma (Evans *et al.*, 1976), but does occur with bladder disease or long-term catheterisation (Spees *et al.*, 1981). Rupture of the bladder has been reported following hydrostatic distension in interstitial cystitis (Higson *et al.*, 1978). Spontaneous bladder rupture, however, has not been previously reported in patients with interstitial cystitis.

Case Report

A 65-year-old lady presented with sudden, constant abdominal pain. She had not passed urine on the day prior to admission. She had not been recently catheterised.

She had previously been investigated for symptoms of repeated urinary tract infections with cystoscopy, which demonstrated a small capacity bladder (100 ml). Biopsies showed non-specific features. Her most recent cystoscopy was over 2 months prior to admission.

On examination she was dehydrated and febrile, with a rigid abdomen. A small volume of thick, purulent, sterile urine was obtained after bladder catheterisation.

At laparotomy the intestine was intact, but a necrotic area was seen at the dome of the bladder with an obvious perforation. The remaining abdominal contents were entirely normal and the bladder perforation was oversewn successfully. She later underwent augmentation cystoplasty. Histology thus obtained showed partial ulceration of benign transitional epithelium with deep fissuring into detrusor muscle and associated hyperplasia of nerves. The detrusor muscle contained numerous mast cells. The appearances were consistent with a diagnosis of interstitial cystitis (Fig.).

Comment

To our knowledge, this is the first reported case of spontaneous bladder perforation associated with interstitial cystitis. The perforation occurred at the apex of one of the fissures in an acute manner. The apex of the fissure was the thinnest part of the bladder wall; the surrounding tissue was relatively ischaemic because of fibrosis and would therefore be most susceptible to perforation if intravesical pressure rose.

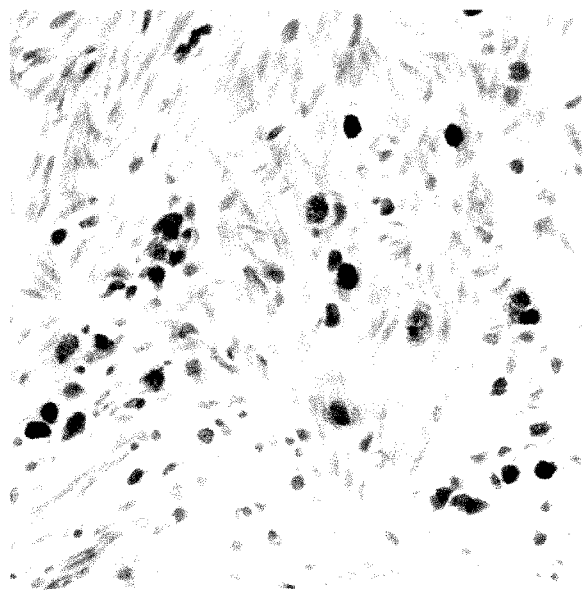


Fig. Detrusor muscle stained with toluidine blue showing mast cells. ($\times 125$).

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Rate of Development of Ureteric Obstruction in Idiopathic Retroperitoneal Fibrosis (Peri-aortitis)

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Before the advent of computed tomography (CT), most patients with idiopathic retroperitoneal fibrosis (peri-aortitis) presented to nephrologists or urologists with unilateral or, more commonly,

bilateral urinary tract obstruction (Baker *et al.*, 1988). With the advent and widespread use of computed tomography, increasing numbers of patients will inevitably present with symptoms of the condition, a peri-aortic mass on CT scanning and without urinary tract obstruction. Such patients present a therapeutic dilemma since little or nothing is known of the natural history of the condition if left untreated. In particular, it is unclear whether the mass should be biopsied at this stage, whether corticosteroid therapy should be administered and whether prophylactic removal of the ureters from likely entrapment by the mass should be carried out. We report a patient who illustrates these dilemmas and provides some insight into the rate of increase in size of a peri-aortic mass and rate of development of urinary tract obstruction.

Case Report

A 57-year-old Saudi businessman developed backache and central abdominal discomfort in January 1987. For several years he had had mild hypertension treated initially with a thiazide and later with enalapril. Investigation elsewhere had revealed elevation of erythrocyte sedimentation rate and diverticular disease of the colon. When first seen in November 1987, general physical examination was normal. Blood pressure was 150/90 mm Hg. ESR was 50 mm/h. Full blood count, blood urea, electrolytes and serum creatinine were normal and creatinine clearance was 80 ml/min. There was no abnormal amount of protein in a 24-h urine collection. He was abacteriuric. Intravenous urography showed normal-sized, unobstructed kidneys. Medial deviation of the ureters was not present. A CT scan was performed in November 1987 (Fig. 1). This showed a peri-aortic mass measuring 5 cm in its maximum transverse diameter and 2.5 cm in its maximum antero-posterior diameter (Fig. 1C). The appearance of the mass was entirely consistent with retroperitoneal fibrosis, although not specific for this diagnosis. The mass enhanced uniformly after intravenous injection of a bolus of contrast medium. At this time, the mass originated at a level 4 cm below the level of the left renal vein and extended inferiorly to below the aortic bifurcation. Although irregular streaks of soft tissue could be identified at a level 3 cm below the left renal vein (Fig. 1B), no discrete soft tissue mass could be identified at this level. Heavy calcification was noted within the wall of the aorta (Fig. 1C). There was no collecting system dilatation (Fig. 1A). No lymphadenopathy or splenomegaly was noted.

Biopsy of the mass was recommended to the patient but he declined this investigation. In the absence of histological proof of the diagnosis, corticosteroid therapy was withheld and he returned home. He returned as a matter of urgency in January 1988. Blood urea was 32.0 mmol/l and serum creatinine 612 μ mol/l. Erythro-

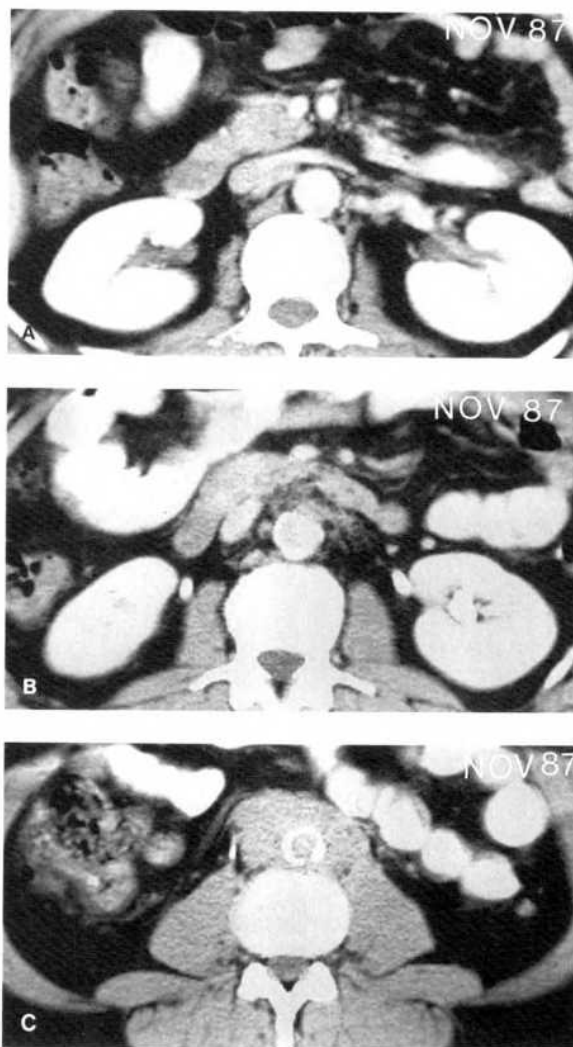


Fig. 1 (A) Axial scan taken through the kidneys at the level of the left renal vein in November 1987 after injection of intravenous contrast medium. Note absence of collecting system dilatation. (B) Scan taken 3 cm inferior to Figure 1A shows no evidence of retroperitoneal or peri-aortic mass, but does show "streaky" linear shadowing in the peri-aortic region. (C) Scan taken below the level of the kidneys showing a large peri-aortic mass surrounding a calcified aorta.

cyte sedimentation rate was 90 mm/h. Full blood count remained normal. He remained abacteriuric. Renal ultrasonography showed bilateral collecting system dilatation. A repeat CT scan was carried out in January 1988 (Fig. 2). This showed a substantial increase in the size of the mass (Fig. 2C); its maximum transverse diameter was now 6.5 cm and the maximum antero-posterior measurement 4 cm. More significantly, the mass had extended superiorly to a level 1 cm below the left renal vein. Thus a scan 3 cm below the level of the left renal vein (Fig. 2B) now showed a discrete peri-aortic mass

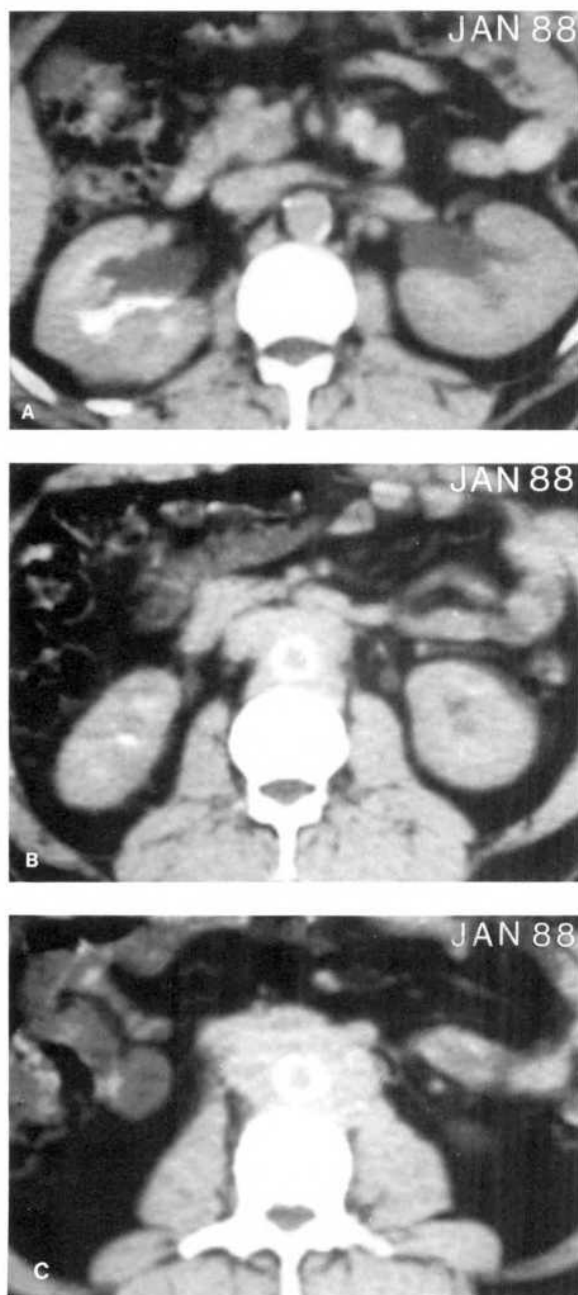


Fig. 2 (A) Axial scan taken in January 1988 at the same level as Figure 1A. Note bilateral collecting system dilatation. (B) Scan taken at the same level as Figure 1B but without injection of intravenous contrast medium. There is now a peri-aortic mass at this level, indicating superior extension of the retroperitoneal fibrosis. (C) Scan taken at the same level as Figure 1C. Note increase in size of the peri-aortic mass.

rather than the ill-defined "streaky" soft tissue shown previously. At this time there was collecting system dilatation (Fig. 2A) due to bilateral ureteric obstruction.

The right kidney was drained by percutaneous nephrostomy with improvement in the uraemic state. Three days later, both ureters were explored through bilateral pararectal Battle incisions. Each ureter was embedded in a mass of fibrous tissue in the area suspected. They were lysed with some difficulty on both sides and displaced laterally, the peritoneum being stitched down to prevent them coming back into the involved area. Histological examination of tissue taken from the retroperitoneal mass at operation showed the typical appearances of benign idiopathic retroperitoneal fibrosis (peri-aortitis). There was no evidence of carcinoma or lymphoma. Two weeks post-operatively he received methylprednisolone 500 mg intravenously on 3 consecutive days and then commenced prednisolone 20 mg daily orally. Three weeks post-operatively, serum creatinine was 135 $\mu\text{mol/l}$ and creatinine clearance 81 ml/min. Subsequently, the dose of prednisolone was reduced in stages so that by May 1989 he was receiving prednisolone 15 mg on alternate days. A CT scan in May 1989 showed a marked reduction in the peri-aortic mass (Figs 3B and C). There was no evidence of urinary tract dilatation (Fig. 3A). In January 1991 he remained well on prednisolone 12.5 mg 3 times a week. Following ureterolysis, ESR had remained consistently below 20 mm/h.

Comment

Idiopathic retroperitoneal fibrosis is, in all probability, an auto-allergic peri-aortitis resulting from leakage of material derived from atheromatous plaques from the aortic wall (Mitchinson, 1984; Parums *et al.*, 1986). Post mortem studies (Mitchinson, 1984) indicate that "sub-clinical periaortitis" has hitherto frequently not been diagnosed in life. With the advent of CT scanning, it is likely that more such patients, whose symptoms may be mild or even non-existent, may present to clinicians. In addition, patients such as ours, in whom symptoms were prominent but urinary tract obstruction was absent, will inevitably be seen more frequently. No consensus exists as to the appropriate investigation and management of such patients since little or no information is available on the natural history of the disorder. One option is to observe the patient with serial clinical assessment, measurement of ESR, assessment of renal function and serial imaging, including CT scanning. The rate at which growth of the peri-aortic mass and entrapment of the ureters occurred in our patient tends to provide an argument against this "wait and see" approach, but whether he is representative of patients with this condition as a whole is unknown. Computed tomography can be used in the follow-up of patients with retroperitoneal fibrosis (Brooks *et al.*, 1987), but serial scans could not be repeated at sufficiently



Fig. 3 Scans performed in May 1989 at the same level as Figures 1A–C and 2A–C. Collecting systems not dilated. Note marked reduction in the size of the peri-aortic mass both in a supero-inferior diameter (compare Figure 3B with 2B) and in the transverse and antero-posterior diameter (compare Figure 3B with 2B).

frequent intervals to assess progress usefully if the rate at which our patient developed a severe clinical problem is typical.

It appears sound practice to confirm the presumptive diagnosis of idiopathic retroperitoneal fibrosis histologically and to exclude the diagnostic possibilities of lymphoma and cancer. Needle biopsy under CT or ultrasound control is technically feasible and safe (Whelan *et al.*, 1991). However, to obtain a biopsy sample sufficiently large to exclude lymphoma or cancer with confidence, laparotomy and open biopsy are usually recommended. This also permits surgical placement of the ureters to a position where entrapment by fibrotic tissue is unlikely. It may be questioned whether laparotomy and biopsy can be justified in a patient in whom clinical, radiographic and CT scan appearances are typical of idiopathic retroperitoneal fibrosis, and in whom corticosteroid therapy alone may resolve the problem without a surgical operation (Baker *et al.*, 1988). Neither clinical, radiological nor CT appearances are specific for idiopathic retroperitoneal fibrosis. This being so, we consider that histological confirmation of the diagnosis should be the rule in patients presenting without ureteric obstruction.

Our observations provide some insight into the rate of growth that may occur in peri-aortic fibrotic tissue in this condition and into the natural history of the disorder. Much more experience of such patients will need to be accumulated before clear management guidelines can be laid down.

Acknowledgement

We thank Mrs Julie Jessop for typing the manuscript.

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Correspondence

Dear Sir,

re Adverse urinary symptoms after total abdominal hysterectomy—fact or fiction? M. D. Griffith-Jones *et al.* *Br. J. Urol.*, 67, 295–297, 1991.

I read with interest the above article, but feel that some points need further clarification.

The exclusion of women with a uterus greater than 10 weeks' size (who are not uncommon in clinical practice) from a study on hysterectomy must result in bias with regard to the incidence not only of pre-operative but also post-operative urinary symptoms. The operation of total abdominal hysterectomy is much easier to perform in a woman with a small uterus, with a concomitant decrease in the disturbance of the para-uterine tissues. This may well result in diminished distortion of uterine and vesical supports, a lower chance of pelvic nerve damage and hence fewer post-operative voiding problems.

The increased incidence of post-operative urinary stress incontinence in the dilatation and curettage (D & C) group is rather puzzling, suggesting perhaps inaccuracy in the pre-operative history given by the patient. I believe this finding highlights the need in this type of study for objective urodynamic evaluation in conjunction with subjective assessment, rather than relying solely on the patient's subjective assessment. In our study (B. T. Parys *et al.* *Br. J. Urol.*, 64, 594–599, 1989) we noted a marked discrepancy of almost 20% between the incidence of urinary symptoms and urodynamically proven dysfunction, emphasising precisely this point.

The explanation for pelvic nerve damage after hysterectomy may lie not only at the sites postulated by A. R. Mundy (*Br. J. Urol.*, 54, 501–504, 1982) but also in that the major part of the vesicourethral innervation enters the bladder at its base, to spread throughout the detrusor muscle. Nerve damage can occur during the blunt dissection of the uterus and cervix uteri/anterior fornix off the bladder base and posterior wall.

Yours faithfully,

B. T. Parys,
Department of Urology, Royal Preston Hospital,
Preston.

Reply from Dr G. J. Jarvis. My co-authors and I feel that two observations must be made on the letter from Mr Parys.

The first observation concerns the criticism of our exclusion of any uterus greater than a 10-week size. The reason for this exclusion was, we felt, obvious. The female pelvis, being bounded by bone, is of a definitive size. A pelvic mass, when it begins to occupy a significant percentage of the pelvis, may cause symptoms by impinging upon local structures, such as bladder or bowel. If we had included in our series of patients undergoing hysterectomy those patients who had a pelvic mass of significant size, and if that pelvic mass were pressing on the bladder and associated with lower urinary tract symptoms, then it is clear that the removal of that pelvic mass might result in the alleviation of those symptoms. Under such circumstances, the patients in the hysterectomy group would have "an unfair advantage" scientifically over the patients in the control group, in that they might have an intrinsic improvement in their lower urinary tract symptoms which might then interfere with the true scientific assessment of the patient's symptoms before and after hysterectomy. It was for this reason that we chose to exclude patients who had a pelvic mass. We should not be criticised for excluding such patients but we should have been severely criticised had we included them.

The second point relates to the accuracy of the pre-operative history. No-one would disagree that objective measurements are superior to subjective symptoms. However, we used subjective symptoms for both the hysterectomy group and the control (D & C) group. All patients had the same history taken, using a highly structured history sheet, and all patients had their histories taken in this fashion by the same group of doctors. My co-authors and I do not see why the pre-operative history taken in this fashion from patients undergoing a D & C should be any the less accurate than that taken from patients undergoing abdominal hysterectomy. We were not looking at absolute history but at the changes in history in the hysterectomy group compared with the D & C group. There may be several possible explanations for our results, but I cannot see how inaccuracy of the pre-operative history could be one of them.

Lastly, I must express some surprise that Mr Parys felt that our prospective controlled study of the symptoms before and after gynaecological surgery should be criticised on the grounds that it is the patient's symptoms which are being compared. The stimulus for me to commence this study

with my co-authors was a retrospective uncontrolled study of lower urinary tract symptoms which patients had attributed to a prior hysterectomy. This study was presented at BAUS in June 1988 and may be found in the British Journal of Urology, **64**, 594–599, 1989. The first author was Mr Parys.

Dear Sir,

re The growing teratoma syndrome. G. M. Jeffery *et al.* *Br. J. Urol.*, **67**, 195–202, 1991.

Jeffery *et al.* have reported a most important series of patients with the growing teratoma syndrome. We present another case where teratoma has grown from microscopic mediastinal disease.

A 25-year-old white man was referred with advanced non-seminomatous germ cell (NSGC) tumour. The primary tumour showed patterns of embryonal carcinoma, mature and immature teratoma and choriocarcinoma. After orchiectomy, AFP and HCG levels were 168 and 642 ng/ml respectively (normal <5 ng/ml). Abdominal CT scan showed a retroperitoneal mass measuring 10.2 cm³. Thoracic CT was normal (Fig. 1). Four cycles of bleomycin/etoposide/cisplatin (BEP) were completed. At the end of chemotherapy AFP and HCG levels were normal. Abdominal CT showed an enlarging tumour of 52.5 cm³ and mediastinal CT revealed a posterior mediastinal tumour of 14.5 cm³ that had not been visible prior to chemotherapy (Fig. 2). Complete resection of these masses



Fig. 2

was performed. They comprised mature teratoma associated with necrosis. The patient is alive and disease-free 26 months after diagnosis.

Complete surgical removal of residual masses after chemotherapy is highly recommended because of the possible persistence of viable tumour and because, despite normalisation of serum markers, CT scan cannot exclude microscopic malignant foci. An enlarging mass may represent residual malignancy but, in some cases, it may contain only mature teratoma—the so-called “growing teratoma syndrome”. In our patient the presence of a posterior mediastinal tumour at the end of treatment, despite a negative CT scan before chemotherapy, proves that mature teratoma may grow from sub-radiological metastases.

The presence of mature teratoma in metastases of germ cell tumours is not understood. It may result either from spontaneous or chemotherapy-induced evolution of a malignant germ cell tumour or arise from a well differentiated lesion which is unresponsive to chemotherapy. Their relative benignity cannot be a reason for therapeutic abstention because some rare cases of metastasising mature teratoma have been described and because de-differentiation into an immature teratoma cannot be excluded. The presence of non-germ cell tumours within germ cell elements is another possibility.

The growing teratoma syndrome occurs in only 5% of patients with advanced NSGC tumours but it must be recognised because of the therapeutic implications. It usually concerns retroperitoneal

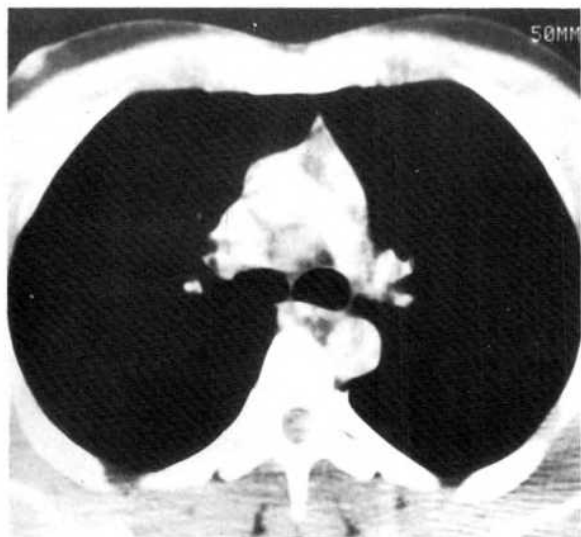


Fig. 1

lymph nodes but the phenomenon can also be seen in mediastinal or lung metastases.

Yours faithfully,

J. F. Berdah, P. Nouyrigat, B. Rouillet and J. P. Olivier
Service de Médecine Interne A and Service de
Radiothérapie-Carcinologie, Centre Hospitalier et
Universitaire Dupuytren, Limoges, France.

Dear Sir,

Determination of pre-orchietomy serum levels of alpha-fetoprotein and human choriogonadotrophin in testicular cancer.

Tumour marker levels are important determinants of treatment in testis cancer. About 70% of non-seminoma patients have elevated alpha-fetoprotein (AFP) and/or human choriogonadotrophin (HCG) before orchietomy, but elevated pre-orchietomy AFP which normalises with a half-life of 5 to 7 days is correlated with a true non-metastatic stage I (Klepp *et al. J. Clin. Oncol.*, **8**, 509–518, 1990).

Between 30 and 40% of patients with early seminoma also have increased HCG levels before orchietomy. Slightly elevated pre-orchietomy HCG which returns to normal after orchietomy (half-life 24–48 h) does not usually change the treatment policy in seminoma patients. Some oncologists apply non-seminoma treatment if particularly high HCG levels are observed in seminoma patients due to the probable existence of unrecognised choriocarcinoma elements.

AFP-producing seminoma is a rare condition (12 of 343 evaluable patients in the combined Medical Research Council/Norwegian Radium Hospital series) and indicates the presence of unrecognised yolk sac tumour elements (Pera *et al. Int. J. Cancer*, **40**, 334–343, 1987). Slightly elevated pre-orchietomy AFP levels in low stage seminoma (< 50 µg/l) usually become normal within 1 to 3 weeks after removal of the primary tumour, even when small retroperitoneal metastases are present. This is the time when the seminoma patient is seen at an oncological clinic for staging and treatment decision. Without the knowledge of the pre-operative AFP levels the routine treatment would be radio-

therapy, but with the information of an elevated pre-orchietomy AFP a patient with low stage seminoma would receive non-seminoma treatment.

In view of the importance of pre-orchietomy tumour marker levels we have reviewed the frequency of pre-orchietomy AFP and HCG determination in 2363 patients in 3 testis tumour registries between 1980 and 1989: 830 patients admitted to the Norwegian Radium Hospital (NRH) with newly diagnosed testis cancer, 880 patients referred to the Royal Marsden Hospital (RMH) after recent orchietomy for testis cancer, and 653 patients from other institutions entered into the Medical Research Council (MRC) surveillance protocol for non-seminoma stage I.

Only 41% of all patients had AFP and HCG measured before orchietomy, with a slight improvement of this percentage during the second 5-year period (Table).

Table Frequency of Determination of Pre-orchietomy Serum Tumour Markers

Years	RMH* (%)	NRH* (%)	MRC† (%)	Total (%)
1980–1984	86/400 (22)	125/430 (29)	111/245 (45)	322/1075 (30)
1985–1989	125/480 (32)	213/400 (53)	276/408 (68)	614/1288 (48)
Total	238/880 (27)	338/830 (41)	387/653 (59)	963/2363 (41)

*All stages. †Stage I only.

In the light of the importance of pre-operative serum marker levels for diagnosis and treatment it is disappointing to learn that this simple test is performed in less than 50% of patients. We therefore encourage urologists to collect serum samples routinely for AFP and HCG measurement in any patient with testicular enlargement and, in particular, before orchietomy for a testicular tumour.

Yours faithfully,

Sophie D. Fossa (Department of Medical Oncology and Radiotherapy, Norwegian Radium Hospital, Oslo, Norway) and M. Mason (Department of Radiotherapy, Royal Marsden Hospital, Sutton, UK).

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21-26 June 1992

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1991. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 10th January 1992.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Scholarships for Experimental and Clinical Research in Urology

The European Association of Urology and the European Board of Urology will award three scholarships for research in Urology. Each scholarship will be awarded for one year, starting on 1 July 1992, at a maximum of 33,000 ECU at any appropriate institution in the world. Further information from: The European Board of Urology Education Committee, P.O. Box 25285, 3001 HG Rotterdam, The Netherlands. Tel: 31.10.436.6665. FAX: 31.10.436.6669.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

British Journal of Urology Travelling Fellowship

This fellowship of £1500 enables a Senior Registrar or numbered Career/Research Registrar to attend the Annual Meeting of the American Urological Association. It is awarded in April each year at the Annual Scientific Meeting of the Senior Urological Registrars Group (SURG). The award is given for the best paper presented at this meeting on a vote by the members of SURG present at the meeting. Invitations to the meeting are sent out in January by the Chairman of the Senior Urological Registrars Group and papers must be new work not previously published and not resulting from a thesis. An additional Fellowship may be awarded at the discretion of the British Journal of Urology and the Senior Urological Registrars Group.

Lewis Medical Travelling Scholarship

The scholarship covers travel, accommodation and registration expenses associated with attending the Annual Meeting of the American Urological Association. The scholarship will be available to any person appointed to a numbered urological training post and will be awarded to the person presenting the winning paper at the Annual Meeting of the Senior Urological Registrars Group. An additional scholarship may be awarded at the discretion of the Senior Urological Registrars Group and Lewis Medical Limited.

Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000 to support a clinical research project. Applicants

should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. The prize will be awarded at the Annual Meeting of the Association.

Canadian Urological Association Meeting

Winnipeg, Canada. 21–25 June 1992

Further particulars from: Dr Denis H. Hosking, GE-446, 700 William Avenue, Winnipeg, Manitoba R3E 0Z3, Canada.

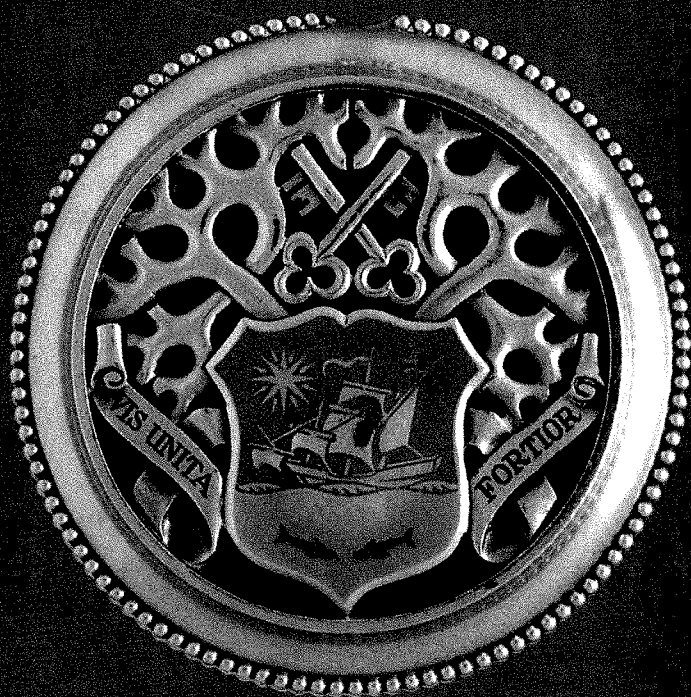
Diary

✶ 1992

- January 10 Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
- March 8–13 19th Biennial Congress of the Urological Association of South Africa, Sun City, South Africa. Contact: Dr I. Lissos, 1 Esselen Towers, Esselen Street, Hillbrow, 2001, South Africa.
- March 19–21 Eleventh International Symposium of Operative Andrology. Istanbul, Turkey. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
- March 19–21 Searching for Prostatic Carcinoma: the Problem of Screening and Early Detection. Munich, Germany. Contact: D. Née, Secretariat, Department of Urology Krankenhaus der Barmherzigen Brüder, Romanstr. 93, W-8000 Munich 19, Germany. Tel: 89/1793-252 or 89/17 56 61. FAX: 89/1782653.
- ✶ March 26–27 Eighth Annual Symposium on Progress in Paediatric Surgery, Oviedo, Spain. Contact: Dr J. L. Teixidor de Otto, Servicio de Cirugía Pediátrica, Hospital Central de Asturias, Centro Universitario, E-33006 Oviedo, Spain.
- April 3–5 Third International Conference on Geriatric Nephrology and Urology. Toronto, Canada. Contact: Dr D. G. Oreopoulos, Peritoneal Dialysis Unit, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8. Tel: 416 364 9974. FAX: 416 360 8127.
- April 9–11 6th International Urological Symposium. Girne, North Cyprus. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
- ✶ April 24–25 Annual Meeting of the Irish Society of Urology. University of Limerick. Contact: Honorary Secretary, Irish Society of Urology, at the Royal College of Surgeons in Ireland, 123 Saint Stephen's Green, Dublin 2, Ireland.
- May 6–8 8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.
- May 10–14 American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
- May 23–24 Société Belge d'Urologie: 57th Congress. Liège, Belgium. Contact: Dr F. F. Wart, 4 Avenue du Bois des Sartis, B-6111 Landelies, Belgium.
- ✶ May 24–28 Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.
- June 4–6 Fourth International Meeting of Andrology, Como, Italy. "Treating Male Infertility: New Possibilities". Contact: Dr G. M. Colpi, II Divisione di Chirurgia, Centro di Andrologia e Infertilità, Ospedale "VALDUCE", Via Dante 11, I-22100 Como, Italy.

- June 10–12 Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.
- June 22–25 Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
- June 23–26 BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
- July 22–25 European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
- August 24–27 Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
- August 24–27 VIIIth International Symposium on Urolithiasis and Related Clinical Research. Cairns, Australia. Contact: Dr Rosemary L. Ryall, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia 5042.
- September 3–6 Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
- September 14–18 Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
- October 9–10 BAUS Autumn Meeting, Swansea. Contact BAUS Office.
- 1993
- May 16–20 American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
- June 20–24 Canadian Urological Association Annual Meeting, Bonaventure Hotel, Montreal, Quebec. Contact: To be announced.
- 1994
- May 15–19 American Urological Association, Moscone Centre, San Francisco, California.

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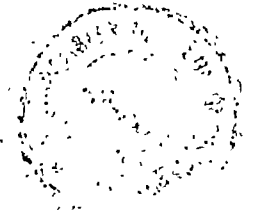
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Manuscripts. Papers should be submitted in Journal style. Failure to do so may lead to significant delays in publication. Papers should be typewritten in double spacing on A4 paper (21 × 29.7 cm) with a margin of at least 3 cm all round. Two copies of the manuscript and illustrations should be submitted and the author should retain a copy for reference.

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Morris, J. A., Oates, K. and Staff, W. G. (1986) Scanning electron microscopy of adenomatoid tumours. *Br. J. Urol.* 58, 183-187.

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REVIEW

Diuresis Renography. Recent Advances and Recommended Protocols

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Diuresis renography is established as a useful test for the investigation of the dilated upper urinary tract (O'Reilly, 1986, 1989). The traditional method involves the administration of a diuretic (frusemide) 20 min into a standard renogram. In this way, the effect of increased urine flow on the rising curve of the dilated renal pelvis or ureter can be demonstrated, the curve continuing to rise in genuine obstruction and falling in a non-obstructed system where the initial appearances were caused by stasis only. Unfortunately, this method results in an equivocal rate of 15% in our hands, and often considerably more in other centres, producing indeterminate washout and an inconclusive result. This, and variable correlation of the test with perfusion pressure flow studies (Hay *et al.*, 1984; Lupton, 1984; Poulsen *et al.*, 1987) stimulated attempts to improve the accuracy of the procedure and minimise the possibility of equivocal responses, measures which have been incorporated into a series of recommended protocols for the performance and interpretation of diuresis renography.

Need for Standardisation

Type of isotope

Several reasons account for the discrepancy in the results obtained by diuresis renography in different centres which, when considered together, make a strong case for standardisation. The widespread use of ^{99m}Tc -DTPA in some European and most American centres can be cited as one of importance. DTPA is completely filtered by the kidneys, a maximum concentration of 5% being reached in 5 min, falling to 2% at 15 min. Where renal function

is poor, however, there is significant extrarenal activity and, in widely dilated systems, accurate area-of-interest mapping between parenchyma and outflow tract can be difficult. The curves are often flatter and less crisp than with ^{123}I -Hippuran, making the differentiation between good and equivocal washout difficult. Curves can be found in the literature which one centre regards as equivocal but which to others appear as non-obstructive, and *vice versa*. The low equivocal rate from Manchester can be attributed in part to the excellent renogram data available from the use of ^{123}I -Hippuran. Of course, ^{123}I is a cyclotron-produced isotope with a short half-life (13.3 h), so that its use is precluded for many centres, particularly those in the USA, where there may be long distances between a particular cyclotron and a clinical nuclear medicine department. This problem may be solved by the arrival of the more easily available ^{99m}Tc -mercaptoacetyltriglycine (MAG3), a new radio-pharmaceutical for renal studies. MAG3 is an analogue of orthoiodohippuran, with about 60% of its clearance; its physiological characteristics are similar, and studies comparing the use of both agents show comparable results (Taylor *et al.*, 1986; Jaffre *et al.*, 1988; Oei *et al.*, 1990). It is likely to be far superior to ^{99m}Tc -DTPA for diuresis renography and will undoubtedly improve data from those institutions using DTPA with disappointing results.

Renal function and rates of urine production

Lack of appreciation of underlying renal function and the flow rates resulting from diuretic administration at varying levels of function also accounts for misunderstanding regarding curve shapes, responses and correlation between diuresis renography and perfusion pressure flow studies. The flow rate induced by the diuretic is a major determinant

Table Clearance Values

Measure of renal function	Time period (min)	Correlation coefficient (r)	Regression equation (CI = creatinine clearance)	Clearance values predicting a total urinary flow rate of 20 ml/min	
				Clearance (ml/min)	Lower 95% confidence limit
Creatinine clearance	3-6	0.66	Flow = CI $\times$ 0.23 + 2.5	77	32
	15-18	0.77	Flow = CI $\times$ 0.26 + 4.0	68	30
^{99m} Tc-DTPA clearance	3-6	0.66	Flow = CI $\times$ 0.55 - 10	56	32
	15-18	0.77	Flow = CI $\times$ 0.44 + 0.5	51	30
¹²³ I-Hippuran clearance	3-6	0.59	Flow = CI $\times$ 0.063 + 1.2	298	115
	15-18	0.71	Flow = CI $\times$ 0.059 + 5.7	269	111

of the renogram curve, but is difficult to quantify, depending on the maturity of the kidneys, the state of the patient's hydration and the underlying renal function. Studies in this centre of the relationship between flow rates and creatinine clearance, ^{99m}Tc-DTPA clearance and ¹²³I-Hippuran clearance have demonstrated linear relationships between each parameter of function and urinary flow rates at 3 to 6 min and 15 to 18 min (see below) after frusemide. The reported correlations (showing 3-6 min flow rates first and 15-18 min second in each case) are: creatinine clearance, $r=0.66$; $r=0.77$; ^{99m}Tc-DTPA clearance, $r=0.66$; $r=0.77$; ¹²³I-Hippuran clearance, $r=0.59$; $r=0.71$. It can be seen that for all parameters a stronger relationship exists with the 15 to 18 min than the 3 to 6 min flow rates. The Table includes, for each parameter of function, clearance values obtained by regression analysis corresponding to a total flow rate of 20 ml/min. It can be seen that a creatinine clearance of 77 ml/min, or (more accurately reflecting glomerular filtration rate (GFR)) a DTPA clearance of 56 ml/min, would be associated with a flow rate of 20 ml/min 3 to 6 min after frusemide. The lower 95% confidence limit of the regression indicates that below a total clearance of 32 ml/min there would be only a 5% chance of achieving this flow rate. Although the confidence limits are wide and the correlations not strong, these data show that if information on underlying renal function is available, single kidney clearance can be derived from the split function data available from the renogram (Brown *et al.*, 1992). It is then possible to assess some measure of the likely urine flow rate during the study. One clinical example of this is if single kidney GFR is less than 32 ml/min, the diuretic-induced flow rate may be sufficient to wash tracer out of the upper tract at that flow rate, giving a non-obstructive result, but since this will undoubtedly

be less than 10 ml/min for the reasons expounded above, the higher flow rate of a perfusion study might be enough to decompensate the same system, give an obstructive result, and demonstrate a lack of correlation between the tests (see below).

Quantification of the urinary flow rates has also been studied by Brown *et al.* (1992). Figure 1 shows the results of an important study in which 86 stable hospitalised patients with indwelling urethral catheters had urine collected at minute-by-minute intervals before and after the administration of 40 mg intravenous frusemide. The average urine flow rates were then plotted against time. It can be seen that there was a rapid increase in flow rate from 3 to 6 min after the injection of frusemide (the period of time the diuretic first influences the rising curve of the renogram in dilated systems). Thereafter there was a more gradual rise in flow rate which stabilised at 15 min and then rose no more. At the time of this study, English *et al.* (1987) and later Upsdell *et al.* (1990) had already developed an alternative diuresis renogram method to try to minimise equivocal cases on the traditional technique by giving frusemide 15 min before the radiopharmaceutical instead of 20 min after it, to try to ensure maximal flow rates during the renogram. The data of Brown *et al.* (1992) demonstrated the validity of this modification, showing a statistically significant increase in flow rate at the 15 to 18 min period after frusemide when compared with the 3 to 6 min period. Upsdell *et al.* (1990) further demonstrated that there was no difference in renogram values for split renal function between these 2 methods—an important point to reassure clinicians that their data on the patients' renal function would be the same regardless of the method used. This work has now led to the introduction of the F-15 renogram (frusemide given 15 min before the radiopharmaceutical) in

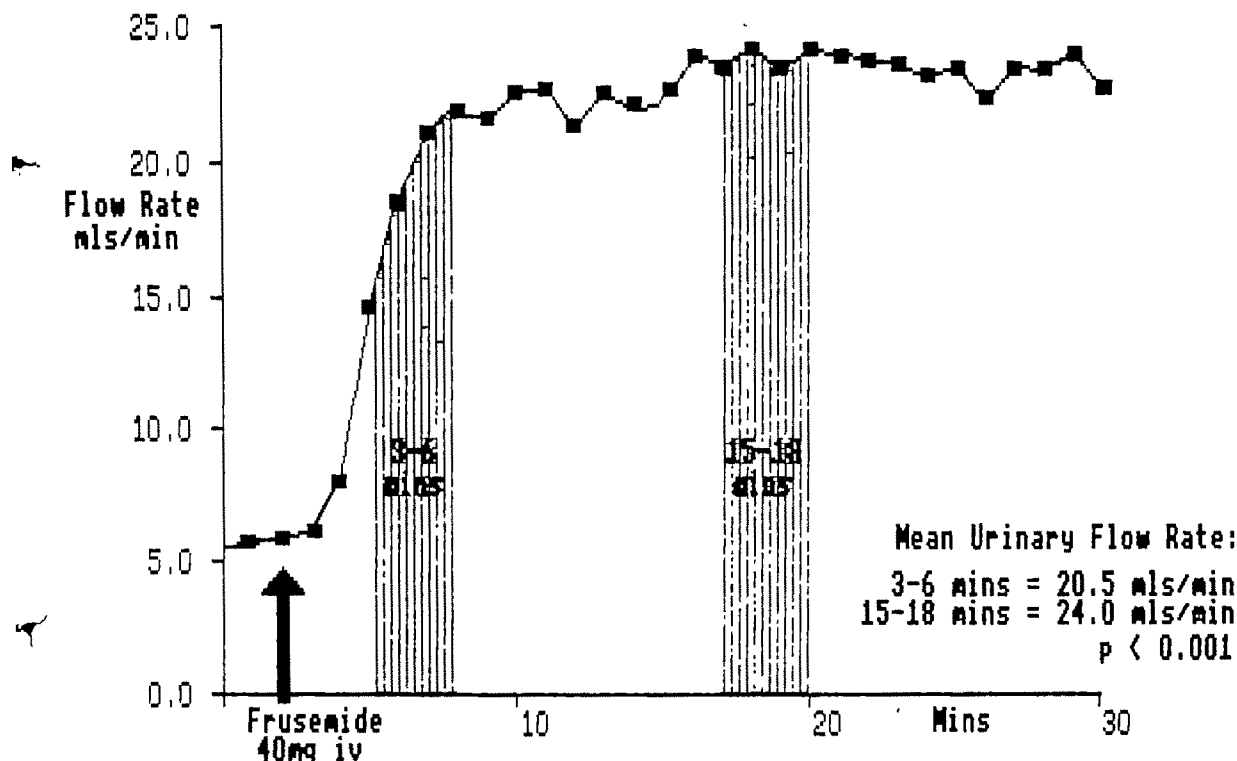


Fig. 1 Average minute-by-minute diuretic-induced flow rates in 86 normal volunteers.

addition to the traditional F + 20 renogram (frusemide given 20 min after the radiopharmaceutical) and Upsdell *et al.* (1990) have provided data to show that the equivocal response rate can be reduced from 17 to 3% by the addition of this modification to the available investigations.

Delayed Double Peak (Homsy's Sign)

The importance of the influence of flow rates on renogram curves can be exemplified by the addition of a new renogram response to the 4 classic examples. In 1988, Homsy *et al.* described a "delayed double peak pattern" on renograms performed in 4 children (Fig. 2) and suggested that this sign might be useful in the diagnosis of intermittent hydronephrosis. Further investigation of this response in our unit has confirmed its validity. We have seen 5 cases in children and adults where what we now refer to as "Homsy's sign" was found; in the 3 cases where it was performed, F-15 renography converted the curve to an obstructed response (Fig. 3). The possible causes of an initially good diuretic response in which excretion ceases half-way down, or even

rises again, are several. A secondary infusion of radiopharmaceutical trapped in the cannula might be persuaded into the circulation by arm movement, but this was excluded in our patients by immediate flushing through of the cannula with saline after the radiopharmaceutical injection; vesicoureteric reflux could be responsible but this was excluded in Homsy's and our own cases by the absence of reflux on cystography, and an indwelling catheter during renography; interference of interaction from activity in the filling bladder would certainly cause this response but this was also excluded by an open indwelling catheter or bladder emptying during scanning. The true cause of this sign, and the reason why it is uncovered by F-15 renography, lie in the urinary flow rates, as shown in Figures 1 and 4. During the resting and early diuretic phases, the pertaining flow can be transported by the pelviureteric junction (PUJ). Eventually, however, the rapid rise in flow rate reaches a level or produces a degree of dilatation such that the particular PUJ under stress cannot transmit the urine load, resulting in decompensation and obstruction, stopping further excretion of tracer, or producing a rise in activity from recirculating tracer. It is now our

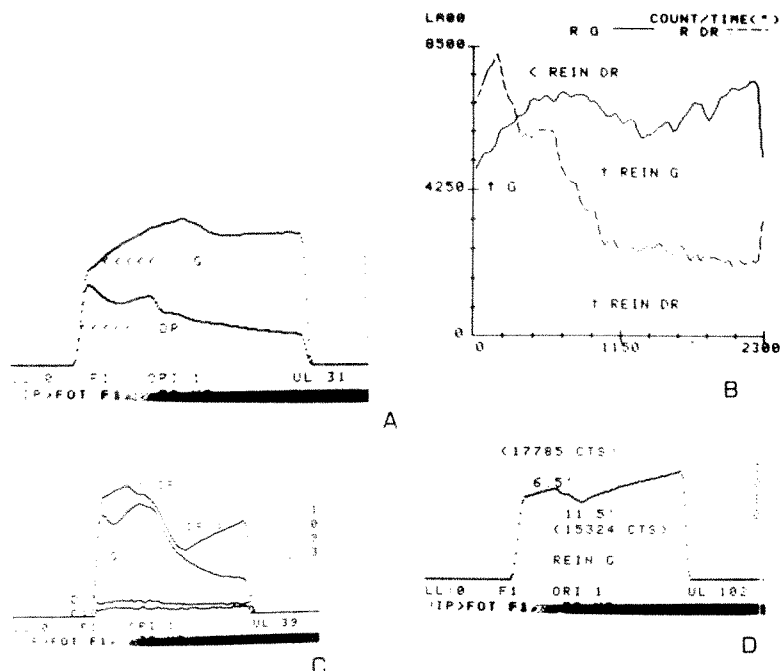


Fig. 2 Original curves described by Homsey showing his delayed double peak response, best seen in C and D. (Reproduced with permission from *J. Urol.*)

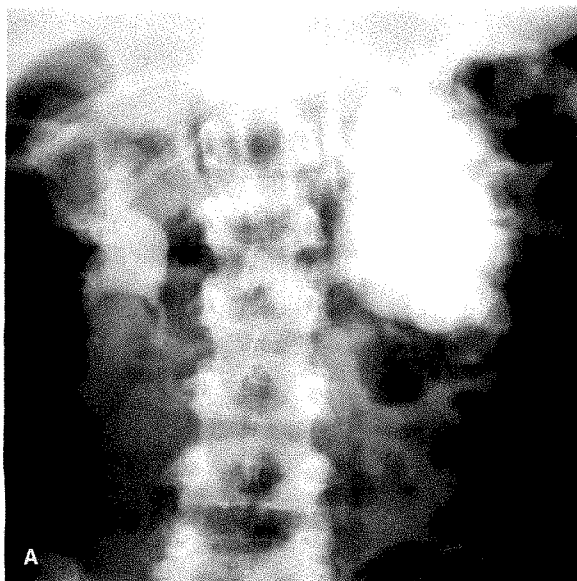
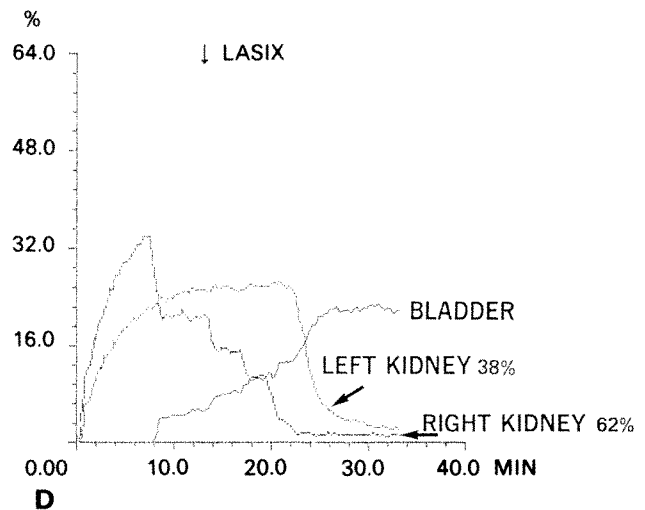
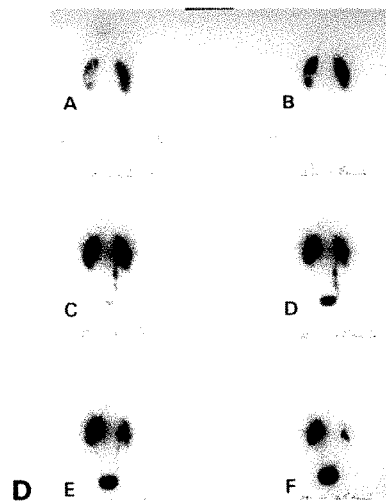
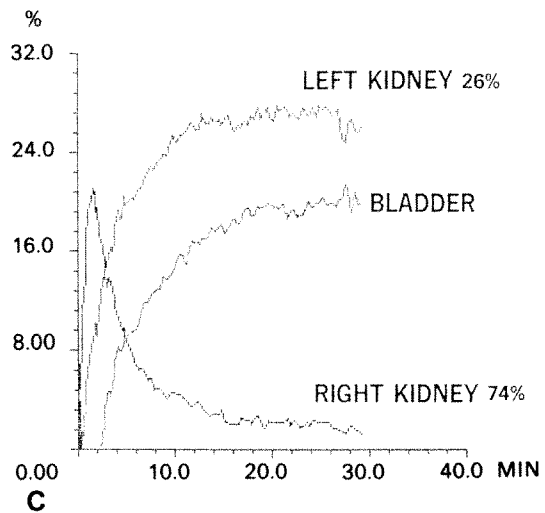
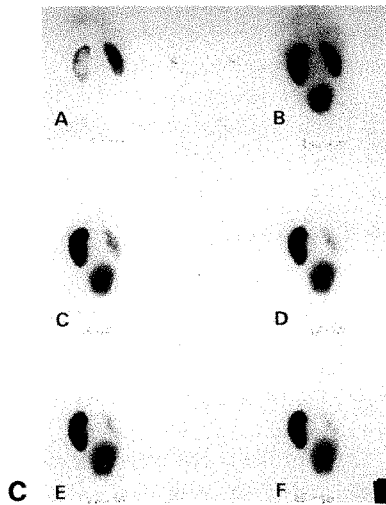
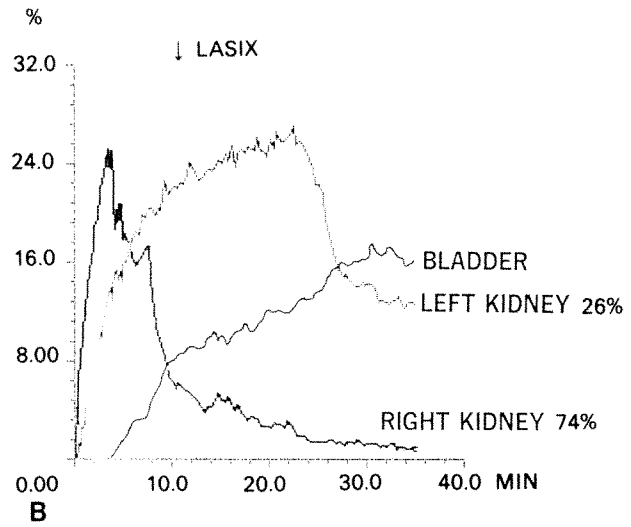
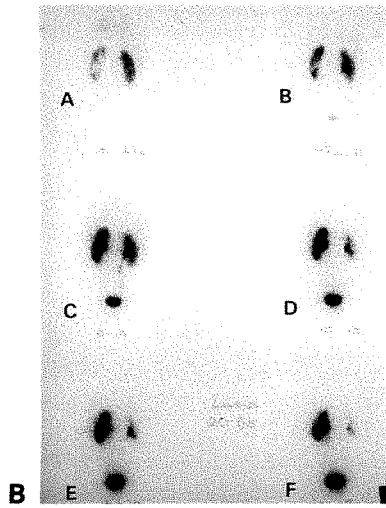


Fig. 3 (A) IVU in 12-year-old child with suspected left PUJ obstruction. (B) F+20 diuresis renogram showing left Homsey's sign. Note how excretion ceases half-way during washout phase, the curve suddenly becoming flat and never getting near to baseline. (C) F-15 diuresis renogram showing conversion of Homsey's sign to obstructed response on left. (D) Post-pyeloplasty F+20 diuresis renogram showing excellent diuretic-induced washout on left with washout curve reaching original baseline. Note enhanced split function value post-operatively.

policy, when this sign is encountered in F+20 renography, to proceed directly to F-15 studies; if the latter are obstructive, surgery is indicated.

The Effect of Bladder/Filling Pressure

The possibility of interactive effects from the bladder on upper tract urodynamics has been known for decades but it is often neglected in clinical investigation. Jones *et al.* (1990) demonstrated the effects of bladder filling on the urodynamics through hydronephrotic kidneys by perfusing a series of 21 hydronephrotic kidneys through a fine bore nephrostomy tube, initially with the bladder on free drainage and subsequently during bladder filling. In 7 patients the renal pelvic pressures were altered by bladder filling reducing upper tract excretion, and loin pain was reproduced in 4 cases. Such interaction had already been demonstrated in animal and model studies (Griffiths, 1987) and in patients with abnormal, poorly compliant bladders (George *et al.*, 1984; Jones *et al.*, 1988) and is not difficult to explain in the presence of a hydroureter given the "open tube" mode of urine transport through dilated upper tracts, permitting proximal pressure transmission. Jones *et al.* (1990) showed that such interaction can also occur when a *normal* ureter intervenes between



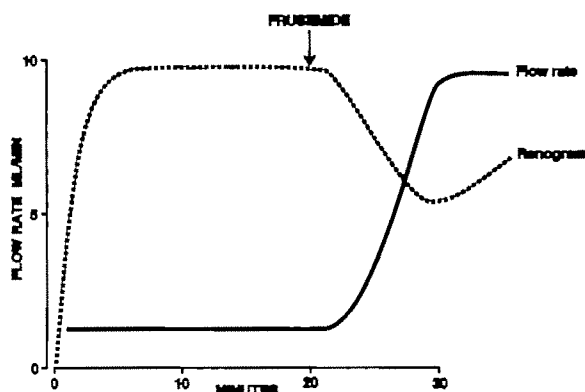


Fig. 4 Relationship between diuretic-induced flow rates and decompensation of renal pelvis (Homsy's sign).

a normal bladder and a dilated renal pelvis, demonstrating that the effect of bladder filling must always be taken into account when applying and interpreting diuresis renography in dilated upper tracts.

Recommendations

Taking the traditional concepts of diuresis renography and the recent advances described above, the following recommendations can be made regarding protocols for performance and interpretation of the test in current clinical practice.

Diuresis renography—Protocols

Hardware/Software

Local Preferences

Pre-examination preparation

Explain procedure, preferably before the patient attends.

Ensure normal hydration (many patients automatically assume they should dehydrate).

Give 500 ml oral fluid load on arrival in department. Ensure patient empties bladder before examination.

Ascertain F + 20 or F - 15 requirement.

Ascertain catheter requirement.

Position

Sitting/erect.

Lying/supine.

Sitting is preferable, since it takes account of the normal hydrostatic component of urine transport. In some circumstances, initial examination supine,

moving then to the erect position, will demonstrate this effect (e.g. positional stasis).

Radiopharmaceuticals

In order of preference:

^{123}I -Hippuran.

$^{99\text{m}}\text{Tc}$ -MAG3.

$^{99\text{m}}\text{Tc}$ -DTPA.

Frusemide

Dosage: 0.5 mg/kg (40 mg in adults).

Administration: 20 min after radiopharmaceutical administration: F + 20.

15 min before radiopharmaceutical administration: F - 15.

In some circumstances (e.g. a very large renal pelvis) some workers have waited 30 or even 40 min to ensure adequate filling before giving the diuretic. If this individual variation is desired, it helps standardisation if the renogram is labelled F + 30 or F + 40 accordingly; this modification is not practised by the author.

F + 20 Diuresis Renography

1. Ensure that the patient is in a good state of hydration and that there is no clinical reason why diuresis should not be induced.
2. Follow the standard renogram procedure (O'Reilly *et al.*, 1986), including pre-examination preparation above.
3. Ask the patient to empty his/her bladder.
4. At 20 min into the test, inject frusemide at a dose of 0.5 mg/kg body weight. Note the time. Continue with renography until significant elimination occurs or until 10 to 15 min after the diuretic was administered; this is vital if late changes, e.g. Homsy's sign, are not to be missed.
5. Measure the volume of urine passed at the end of the test to estimate flow rate and exclude dehydration effect.
6. Warn the patient that the effect of diuresis will last for an hour or two.

F - 15 Diuresis Renography

1. Ensure that the patient is in a good state of hydration and that there is no clinical reason why diuresis should not be induced.
2. Ask the patient to empty his/her bladder.
3. Insert a butterfly needle into a suitable vein.

Inject frusemide at a dose 0.5 mg/kg body weight. Wait 15 min before starting step 4.

4. Inject the radiopharmaceutical as for a routine renogram.
5. Continue the renogram as normal. If the patient needs to pass urine in the middle of the test, leave the system running and reposition after the patient returns. Continue the renogram until 20 min after the radiopharmaceutical injection.
6. Measure the volume of urine voided.
7. Warn the patient that the effect of the diuresis will last for an hour or two.

Combined F + 20 and F – 15 Diuresis Renography

This method may only be used if most of the activity has been excreted from the kidneys by the end of the routine F + 20 renogram.

1. Check that the patient is in a good state of hydration and that there are no clinical reasons why diuresis should not be induced.
2. Perform a standard F + 20 diuresis renogram.
3. If 15 min after the injection of frusemide most of the activity has left the kidneys, inject a further dose of radiopharmaceutical. A second dose equal to the first dose should be sufficient. Thus an F – 15 study is initiated.
4. Continue the renogram as from step 5 in the F – 15 diuresis renography protocol.

Role of Indwelling Catheter

A full or filling bladder may affect upper tract emptying in some cases. This can be avoided by an indwelling open catheter, but a catheter may not always be desirable or necessary.

The interactive effect of the bladder on renal emptying can be displaced by getting the patient to pass urine after 20 min in a standard renogram, or 10 min after frusemide, and continuing data collection for a further 10 min. Assuming that there is no voiding dysfunction, this will reflect urodynamic changes in the upper tract consequent on lower tract emptying. This is particularly important when analogue images show retention of tracer in a dilated upper tract after frusemide.

Certain groups of patients will require a renogram with an indwelling catheter if accurate reflection of upper/lower tract interaction is to be obtained.

These include:

- Patients with lower tract obstruction.
- Patients with demonstrable residual urine.
- Patients with known voiding difficulties.

Patients with neuropathic bladders.

Patients with vesicoureteric reflux.

Patients with unexpected (obstructive) renogram results.

It may be necessary to perform renography with a full and an empty bladder for absolute diagnostic accuracy.

Diuresis Renography—Interpretation

Normal response before diuresis

Normal at normal resting flow rates. The possibility exists that the system could decompensate and obstruct at diuretic flow rates. This is rare.

Obstructive response

A false positive result may occur in hugely dilated upper tracts which even diuretic-induced flow rates may not fill for the duration of the test (*e.g.* the huge ureters of prune belly syndrome). Such cases are a small minority. In general,

If $SKGFR > 32$ ml/min, an obstructive response = obstruction.

If interactive bladder effect is suspected, test should be repeated with indwelling catheter.

If $SKGFR < 32$ ml/min, the result must be scrutinised.

It may be obstructed but there may have been insufficient increase in flow to wash out the tracer. An F – 15 study may be useful but there may not be much increase in flow over the F + 20 where function is poor.

Remember, huge capacities, very poor renal function, bladder interaction and dehydration are the main causes of a falsely positive diuresis renogram.

Non-obstructive response

Non-obstructive washout indicates that the kidney is not obstructed *at that flow rate*.

If $SKGFR > 32$ ml/min, then the flow rate should be comparable to that pertaining during a Whitaker test. Washout at this GFR should exclude significant obstruction but not exclude decompensation at higher flow rates.

If $SKGFR < 32$ ml/min, then the flow rate through the upper tract may be less than 10 ml/min and the system might decompensate at a higher flow rate, *e.g.* during a Whitaker test.

Equivocal response

If $SKGFR > 32$ ml/min, then sub-total washout (an equivocal response) probably indicates sub-total

obstruction. To clarify the situation, an F-15 renogram should be performed.

If SKGFR < 32 ml/min, then sub-total washout is an inconclusive result, probably due to sub-total diuretic response. An F-15 renogram may help but is unlikely to produce an enhanced diuresis as function becomes poorer. This is a truly equivocal result.

The role of the F-15 renogram

As No. 1 choice if only one opportunity exists to distinguish between obstructive and non-obstructive dilatation.

To clarify F+20 diuresis renograms in equivocal or unexpected responses by examining the effect of increased flow rate on the curve.

The reason for not recommending the F-15 diuresis renogram as a complete replacement for the F+20 test is that the latter demonstrates the urodynamics through the upper tract without any modification or manipulation. Thus it can be seen if the test is normal, the result of stasis, the result of Homsy's phenomenon, etc. This is a purist, academic approach, however, and there is no contraindication to the F-15 technique being used as the first approach.

The role of renal function assessment

To establish baseline split renal function.

To investigate post-operative improvement in split function.

To provide data on single kidney GFR for interpretation.

To assist in conservative management of equivocal cases.

Note that there is no significant difference between split function values in F+20 and F-15 diuresis renograms, so the 2 techniques are interchangeable and comparable in terms of renal function determination.

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The Importance of Renal Function in the Interpretation of Diuresis Renography

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Summary—Interpretation of the diuresis renogram is dependent on a full understanding of the factors that contribute to the washout curve, a major determinant being the urinary flow rate induced by the diuretic. Frusemide-induced flow rates were measured in 86 patients over a 30-min period and related to creatinine clearance in 39, ^{99m}Tc -DTPA clearance (glomerular filtration rate (GFR)) in 27, and ^{123}I -Hippuran clearance (effective renal plasma flow) in 20. The flow rates 3 to 6 min and 15 to 18 min after administration of the diuretic received specific attention because of their importance to F + 20 and F – 15 diuresis renography respectively. The mean urinary flow rate 15 to 18 min after frusemide was 3.5 ml/min greater than at 3 to 6 min ($P < 0.001$), explaining the value of the F – 15 renogram in further evaluating equivocal F + 20 curves. Linear relationships were observed between each parameter of function and the 3 to 6 min and 15 to 18 min periods as follows: creatinine clearance $r = 0.66$, $r = 0.77$; ^{99m}Tc -DTPA clearance $r = 0.66$, $r = 0.77$; ^{123}I -Hippuran clearance $r = 0.59$, $r = 0.71$. From regression analysis of the data presented it is possible, with knowledge of total and split function, to predict single-kidney flow rates. It is demonstrated that these may commonly exceed flow rates used for perfusion studies if function is normal, but a single-kidney flow rate of 10 ml/min is unlikely to be attained if the single-kidney GFR is less than 15 ml/min.

Over the last decade, diuresis renography has become an established method for investigating dilatation of the upper urinary tract (O'Reilly *et al.*, 1979). A dilated collecting system may be confirmed as obstructed, or a convincing washout may occur in response to the administration of a diuretic 20 min after the radiopharmaceutical (F + 20 diuresis renography). In approximately 15%, an equivocal response is obtained. Such cases can be further evaluated by employing the modification of injecting the diuretic 15 min before the radiopharmaceutical (English *et al.*, 1987). By using this technique, referred to as F – 15 diuresis renography, the radiopharmaceutical injection coincides with the time of maximum diuresis, and a proportion of systems equivocal on F + 20 renography are converted to an obstructed or non-obstructed pattern by the increased urinary flow rate.

The urinary flow rate induced by the diuretic injection is a major determinant of the renogram curve. The flow response to the diuretic is itself dependent on a number of factors, including the level of renal function and the state of hydration and maturity of the kidneys. The significance of renal function has been highlighted in a preliminary report in which we investigated the relationship between creatinine clearance and urinary flow rates induced by frusemide under conditions simulating diuresis renography (Upsdell *et al.*, 1988). This report presents the completed study, examining the relationship between diuretic-induced urinary flow rates and 3 determinants of renal function: creatinine clearance, ^{99m}Tc -DTPA clearance and ^{123}I -Hippuran clearance. The study is confined to adult kidneys. We set out to investigate the extent to which urinary flow rates may be predicted from knowledge of prevailing renal function and the relevance that this may have to the interpretation of the renogram curve, particularly in the light of

reported discrepancies between diuresis renography and perfusion pressure flow studies.

Patients and Methods

A total of 84 male and 2 female patients participated in the study after giving fully informed consent. All had indwelling urethral catheters either prior to or following elective surgery, were in a stable medical condition and had normal upper tract appearances on urography. Each patient was encouraged to drink for the period prior to the study; 15 min before commencing, each patient was given 500 ml of water in accordance with the standard protocol for renography adopted in this unit. Patients were then placed supine, the catheter bags disconnected and the bladder allowed to empty until a steady flow rate was established. Minute-by-minute urinary flow was then measured for a 30-min period using graduated measuring cylinders. Frusemide, 40 mg, was injected intravenously after the second min.

Twenty-four-h creatinine clearances were performed in 39 patients. The urine collections were made through the catheter and timed to end just before the start of the flow rate analysis when the plasma sample was taken. In 27 patients a more accurate measure of glomerular filtration rate was obtained by measuring the plasma clearance of ^{99m}Tc -diethylene triamine penta-acetic acid (^{99m}Tc -DTPA), using a 2-sample, single-injection method. In the remaining 20 patients, effective renal plasma flow was measured as the clearance of ^{123}I -Hippuran at the time of standard renography using the single-sample V_{44} method (Tauxe *et al.*, 1971). In all but 2 cases, clearance studies were performed on the same day as flow rate measurements.

As adopted in the preliminary report, the urinary flow rates 3 to 6 min and 15 to 18 min after injection of the diuretic were chosen for detailed analysis (Fig. 1). The 3 to 6 min interval is of most relevance to standard F+20 diuresis renography when the early effect of the diuretic on the rising curve is under study. The 15 to 18 min period reflects the diuresis achieved at the time of injection of the radiopharmaceutical for F-15 diuresis renography.

Results

The mean urinary flow rate for the patients over the 30-min collection period is shown in Figure 2. It can be seen that the first effect of the diuretic was

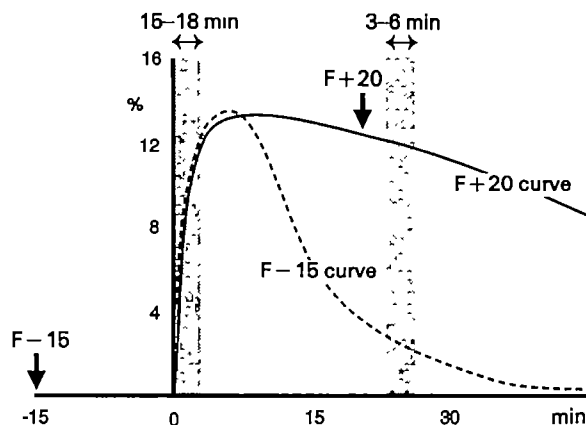


Fig. 1 Time intervals following diuretic injection: 3 to 6 min of relevance to F+20 diuresis renography; 15 to 18 min to F-15 diuresis renography.

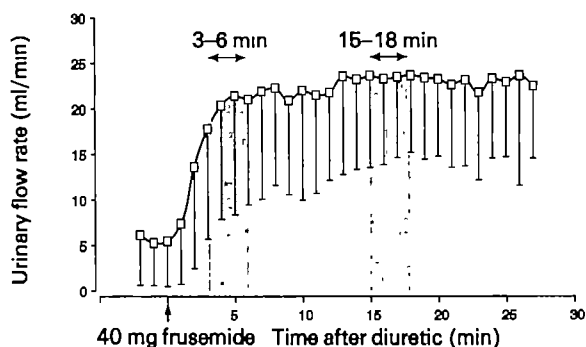


Fig. 2 Mean urinary flow rates following diuretic injection. (Error bars indicate standard deviation).

observed during the third min. The mean flow rate continued to rise through the 3 to 6 min period, peaking at or just before the 15 to 18 min period. The mean urinary flow rate for the 3 to 6 min period was 20.5 ml/min (range 2.5-50.0) and at 15 to 18 min was 24.0 ml/min (range 8.5-42). This difference of 3.5 ml/min between the 2 time periods was highly significant ($P < 0.001$).

A linear relationship was observed between each parameter of renal function and the urinary flow rates for the 2 time intervals studied. Table 1 gives the product-moment correlation coefficients for the relationships between the creatinine, ^{99m}Tc -DTPA and ^{123}I -Hippuran clearances, and the mean urinary flow rates 3 to 6 min and 15 to 18 min after diuretic injection. Typical scattergraphs are given in Figure 3, ^{99m}Tc -DTPA clearance versus the 15 to 18 min flow rate, the strongest correlation obtained, and Figure 4, ^{123}I -Hippuran clearance

Table Relationship between Urinary Flow rates and Parameters of Renal Function

Measure of renal function	Time period (min)	Correlation coefficient (r)	Regression equation	Clearance values predicting a total urinary flow rate of 20 ml/min	
				Clearance (ml/min)	Lower 95% confidence limit
Creatinine clearance	3-6	0.66	Flow = Cl $\times$ 0.23 + 2.5	77	32
	15-18	0.77	Flow = Cl $\times$ 0.26 + 4.0	68	30
^{99m} Tc-DTPA clearance	3-6	0.66	Flow = Cl $\times$ 0.55 - 10	56	32
	15-18	0.77	Flow = Cl $\times$ 0.44 + 0.5	51	30
¹²³ I-Hippuran clearance	3-6	0.59	Flow = Cl $\times$ 0.063 + 1.2	298	115
	15-18	0.71	Flow = Cl $\times$ 0.059 + 5.7	269	111

versus the 3 to 6 min flow rate, the weakest. For all parameters of renal function studied, a stronger relationship was observed with the 15 to 18 min urinary flow rate than with the 3 to 6 min. This may reflect variation in the time taken to respond to frusemide and the increased influence of kidney to bladder transit times at lower flow rates. A better relationship was observed between GFR and flow

rate than between ERPF and flow rate, and was evident even when the smaller numbers in the ERPF group were taken into consideration.

Discussion

Diuresis renography will give an unequivocal result for clinical guidance in approximately 85% of cases, and this figure can be further increased by employing the F-15 modification. There is, however, considerable disagreement between results of diuresis renography and perfusion pressure flow studies. In recent series, agreement has varied between 53% (Whitaker and Buxton-Thomas, 1984) and 85% (Kass *et al.*, 1985), with underestimation and overestimation of obstruction relative to both techniques.

The underlying principles of the 2 methods are, however, very different. The perfusion pressure flow study, or Whitaker test, is a measure of outflow resistance to artificial perfusion of the renal pelvis and is unrepresentative of any other physiological parameters. The curve of the diuresis renogram is dependent on the tracer used, the state of hydration and the level of renal function. Both are dependent on the shape and size of the renal pelvis, its outflow resistance, gravity and bladder filling. It is only by careful consideration of all of the contributory factors, with standardisation of as many as possible, that a confident interpretation can be made. The complexity introduced by this multiplicity of factors is matched only by the inaccuracies that can be introduced by ignoring physiological parameters when interpreting perfusion pressure flow studies.

The level of renal function is a major determinant of the diuresis renogram curve, but one that cannot be standardised. It is therefore necessary to be able to use available information regarding renal function to predict the likely response of the kidney during the investigation. The most important

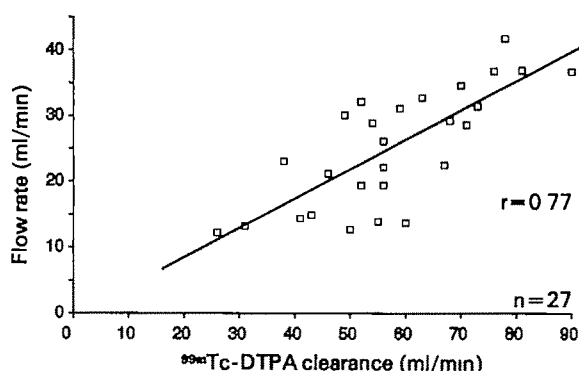


Fig. 3 ^{99m}Tc-DTPA clearance versus urinary flow rate 15 to 18 min after frusemide.

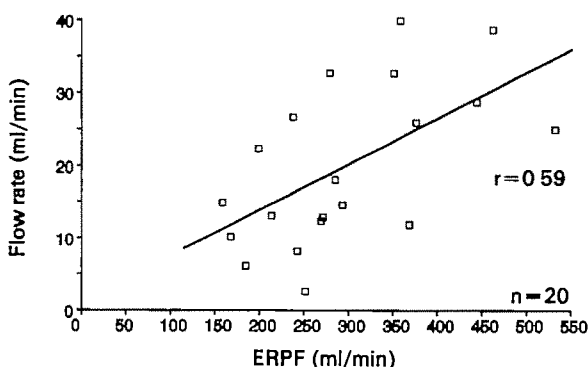


Fig. 4 ¹²³I-Hippuran clearance versus urinary flow rate 3 to 6 min after frusemide.

consequence of function is the flow rate achieved during forced diuresis and is the subject of this study.

The significant increase in flow rate 15 to 18 min after diuretic compared with 3 to 6 min provides an explanation for the increased discriminatory value of the F-15 renogram in the further evaluation of equivocal F+20 renogram curves. An additional 1 or 2 ml/min flow rate at the time of radiopharmaceutical injection may be just sufficient to exceed the capacity of an already equivocal outflow and lead to decompensation and a characteristic obstructed curve.

Patients studied had no lateralising pathology, and if an equal contribution is assumed from both kidneys, it can be seen from Figure 2 that single-kidney flow rates are commonly in excess of the 10 ml/min used routinely for perfusion flow studies. From the regression data in Figure 3, a single-kidney flow rate of 20 ml/min or more is to be expected in a young adult with normal renal function, and at least 15 ml/min in a patient with a total GFR in the order of 70 ml/min.

The Table includes, for each parameter of renal function, clearance values obtained by regression analysis which corresponds to a total urinary flow rate of 20 ml/min, *i.e.* the single-kidney flow rate of 10 ml/min of the perfusion pressure flow study. It can be stated, for example, that a creatinine clearance of 77 ml/min or a ^{99m}Tc -DTPA clearance of 56 ml/min would be associated with a total urinary flow of 20 ml/min 3 to 6 min after diuretic. The lower 95% confidence limit of the regression indicates that below a total clearance of 32 ml/min (or a single-kidney clearance of 16 ml/min) there would be only a 1 in 20 chance of achieving this flow rate; 15 to 18 min after frusemide the corresponding clearance values are less, but because of the tighter distribution there is little difference in the lower 95% confidence limits. The differences in the figures for creatinine clearance and ^{99m}Tc -DTPA clearance reflect the tendency for creatinine clearance to overestimate GFR because of a variable degree of tubular secretion.

The correlations are not strong and the confidence limits are wide. None the less, these data have immediate implications for the interpretation of the diuresis renogram. If functional information is available from a creatinine clearance, or ^{99m}Tc -DTPA or Hippuran clearance from the radiopharmaceutical injected for the renogram itself, the individual single-kidney clearance can be derived from the split function data. It is then possible to obtain some idea of the likely flow rate in the system

under study. If single-kidney GFR is, for example, less than 28 ml/min, an F+20 diuresis renogram may wash out normally with a flow rate less than 10 ml/min, but the same system may exhibit a high perfusion pressure at a steady flow of 10 ml/min during a Whitaker test. This situation may in part explain cases of "low grade pelviureteric obstruction" as described by Wacksman *et al.* (1986). Every system has its maximal transmission rate above which it will decompensate. If, however, physiological flow rates do not exceed this maximum, there may be no grounds for surgical intervention unless symptoms and functional loss can be demonstrated.

The converse is also true. A narrowed pelviureteric outlet in a healthy young adult may have a maximum transmission rate of 20 ml/min. From this study it is clear, however, that the single-kidney flow rate may well exceed this during, for example, a forced alcoholic diuresis. Under these circumstances a positive diuresis renogram may be obtained, but pressure rises during a Whitaker test are not encountered until the flow rate is increased to 20 ml/min or more.

In conclusion, urinary flow rates are maximal 15 min after diuretic injection, explaining the advantage of F-15 diuresis renography over standard F+20 renography in the investigation of equivocal washout. Urinary flow rates vary considerably in response to forced diuresis, but are related to renal function. Knowledge of the latter enables a more critical interpretation of the renogram curve. Single-kidney flow rates in patients with normal function may greatly exceed the flow rates routinely used for perfusion pressure flow studies. Below a single-kidney GFR of 15 to 16 ml/min it would be very unlikely for a flow rate of 10 ml/min to be achieved. Attention to the physiological principles underlying the available tests for the assessment of urinary tract dilatation is necessary to achieve the most reliable interpretation of their results.

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The F-15 Diuresis Renogram in Suspected Obstruction of the Upper Urinary Tract

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Summary—The results are presented of the first long-term follow-up study of patients with suspected obstruction of the upper urinary tract investigated by a modified form of diuresis renography (F-15 renography). The incidence of equivocal results from diuresis renography is significantly reduced by the use of the F-15 renogram.

F-15 renography provides a reliable assessment of the upper urinary tract in patients with suspected obstruction and is recommended in the investigation of equivocal upper urinary tract dilatation.

Diuresis renography is widely accepted in clinical practice for the investigation of dilated upper urinary tracts. Despite over 12 years' experience with this technique, however, equivocal results are still obtained in up to 17% of cases (Upsdell *et al.*, 1990). For several years we have been investigating a modified method of diuresis renography in which frusemide is given intravenously 15 min before the radiopharmaceutical (English *et al.*, 1987), a technique which we refer to as F-15 renography. This timing of frusemide has been shown to maximise urinary flow rates (Upsdell *et al.*, 1988; Brown *et al.*, 1992). We report the results of the first long-term follow-up study of 50 patients investigated by this technique and discuss the clinical indications for F-15 diuresis renography.

Patients and Methods

All patients under the care of a single Department of Urology who were initially investigated for suspected obstruction of the upper urinary tract by both standard and F-15 diuresis renography were entered into the study. Between 1982 and 1987 70 such patients were seen in this department. On follow-up, 2 had died of non-renal causes, 1 was pregnant, 1 declined further follow-up owing to severe arthritis and reduced mobility and 16 had

either moved out of the area or defaulted. This left 50 patients, 13 male and 37 female, with 55 symptomatic kidneys available for review. Their ages ranged from 22 to 69 years (mean 40). All patients had suspected obstruction of the upper urinary tract on clinical and/or radiological grounds. All underwent initial assessment by standard gamma camera renography (O'Reilly *et al.*, 1978), followed by F-15 renography in which frusemide is given intravenously in a dose of 0.5 mg/kg body weight 15 min before the radiopharmaceutical (English *et al.*, 1987). All scans were performed using ^{123}I -Hippuran (0.2 MBq/kg body weight) with the patient sitting in front of a gamma camera. The acquired data were analysed using an MDS computer.

Four patterns of elimination were identified during the standard diuresis renograms as described by O'Reilly *et al.* (1978), *i.e.* unobstructed (type I), obstructed (Type II), hypotonic (Type IIIa) and equivocal (Type IIIb). In F-15 renography only 3 types of washout curve are identified, namely unobstructed, obstructed and equivocal. The subsequent management of all patients was based on clinical signs and symptoms and the results of the initial F-15 renogram. At the conclusion of the study all patients underwent further clinical, biochemical and renographic assessment. The time between the initial F-15 renogram and the final renographic assessment ranged from 1 to 7 years,

with a mean follow-up of just over 4 years (50 months). Only 4 patients had a follow-up period of less than 24 months.

Results

Initial renographic assessment and management

There were 32 cases of unequivocal washout on standard diuresis renography (9 unobstructed, 19 hypotonic and 4 obstructed). The results of the F-15 renogram agreed with the standard diuresis renogram in all 9 unobstructed cases and these patients were all treated conservatively. Of the 19 patients thought to have hypotonic washout by standard diuresis renography, 16 were confirmed as unobstructed by F-15 renography and all were initially treated conservatively, although 1 patient re-presented after 3 years with recurrent loin pain and underwent pyeloplasty without further renographic assessment. However, 2 kidneys thought to have hypotonic washout on standard diuresis renography were judged to have equivocal washout by F-15 renography and underwent pyeloplasty for continuing symptoms. Furthermore, one kidney considered to have hypotonic unobstructed washout by standard diuresis renography was shown to be obstructed on F-15 renography (Fig. 1) and underwent pyeloplasty, at which time prominent aberrant lower pole vessels were demonstrated crossing the pelviureteric junction.

Obstructed washout (Type II) was seen in 4 kidneys on the initial standard diuresis renogram and all of these were confirmed as obstructed by the F-15 renogram. Two of these kidneys underwent pyeloplasty, 1 percutaneous pyelolithotomy and 1 nephrectomy after failed pyeloplasty.

Equivocal washout (Type IIIb) was demonstrated in 23 cases using standard diuresis renography. The F-15 renogram clarified washout in 21 of these. Thirteen were shown to be unobstructed by the F-15 renogram (Fig. 2) and were treated conservatively. Eight kidneys were shown to be obstructed by the F-15 renogram; 4 of these underwent pyeloplasty, 2 required nephrectomy, 1 patient passed an obstructing stone, and 1 patient with spina bifida and multiple medical problems was treated conservatively. Only 2 kidneys remained equivocal after F-15 renography and both of these were treated conservatively.

Final outcome, including renographic assessment and symptoms

A total of 39 cases were considered to be unobstructed on the initial F-15 renogram. All of these

were treated conservatively and at final assessment the elimination pattern had changed in only 1 patient; this was due to an undiagnosed asymptomatic stone moving down into the ureter causing obstruction. The remaining 38 cases with an unobstructed F-15 renogram remained unobstructed. There was a significant loss of relative function ($>5\%$) in 4 patients. However, 2 of these had chronic stone disease and 1 had undergone surgery to that kidney, leaving only 1 with an unexplained loss of relative function. The drop in relative function in this case was 7% which, although renographically significant, is unlikely to have any clinical significance. 21 patients who had unobstructed F-15 renograms were completely symptom-free at follow-up. A further 9 patients had identifiable non-renal disease as the cause of their original symptoms (5 orthopaedic, 2 gynaecological and 2 gastrointestinal). Nine patients had persistent symptoms suggesting a renal origin; in 5 of these the symptoms were due to identifiable renal disease (3 recurrent urinary tract infections, 2 recurrent stone formers), and a further patient, who has already been mentioned, underwent a pyeloplasty but continues to have intermittent loin pain. This leaves 3 patients with persistent unexplained pain of presumed renal origin in whom there has been no change in drainage pattern or deterioration in relative function since initial assessment.

All patients with obstructed F-15 renograms at initial assessment who underwent corrective surgery showed an improvement in drainage, with relative function either improved or stable at follow-up assessment. Furthermore, all of these patients were free of renal pain except for one who was passing "gravel" intermittently in his urine. The 2 stone patients (1 passed his stone spontaneously and the other required percutaneous nephrolithotomy) were symptom-free with improvement in both drainage and function. The spina bifida patient who was unfit for surgery, and was therefore treated conservatively, remains obstructed with loss of renal function in that kidney.

The 2 patients with equivocal F-15 renograms who were treated conservatively had stable renal function and stable or improved drainage. One was completely symptom-free whilst the other suffered from recurrent urinary tract infections and abdominal pain thought to be gastrointestinal in origin. The remaining 2 equivocal patients underwent pyeloplasty. One of these had a good result in terms of increased relative function but continued to complain of recurrent renal pain. The drainage pattern of the F-15 renogram remained equivocal

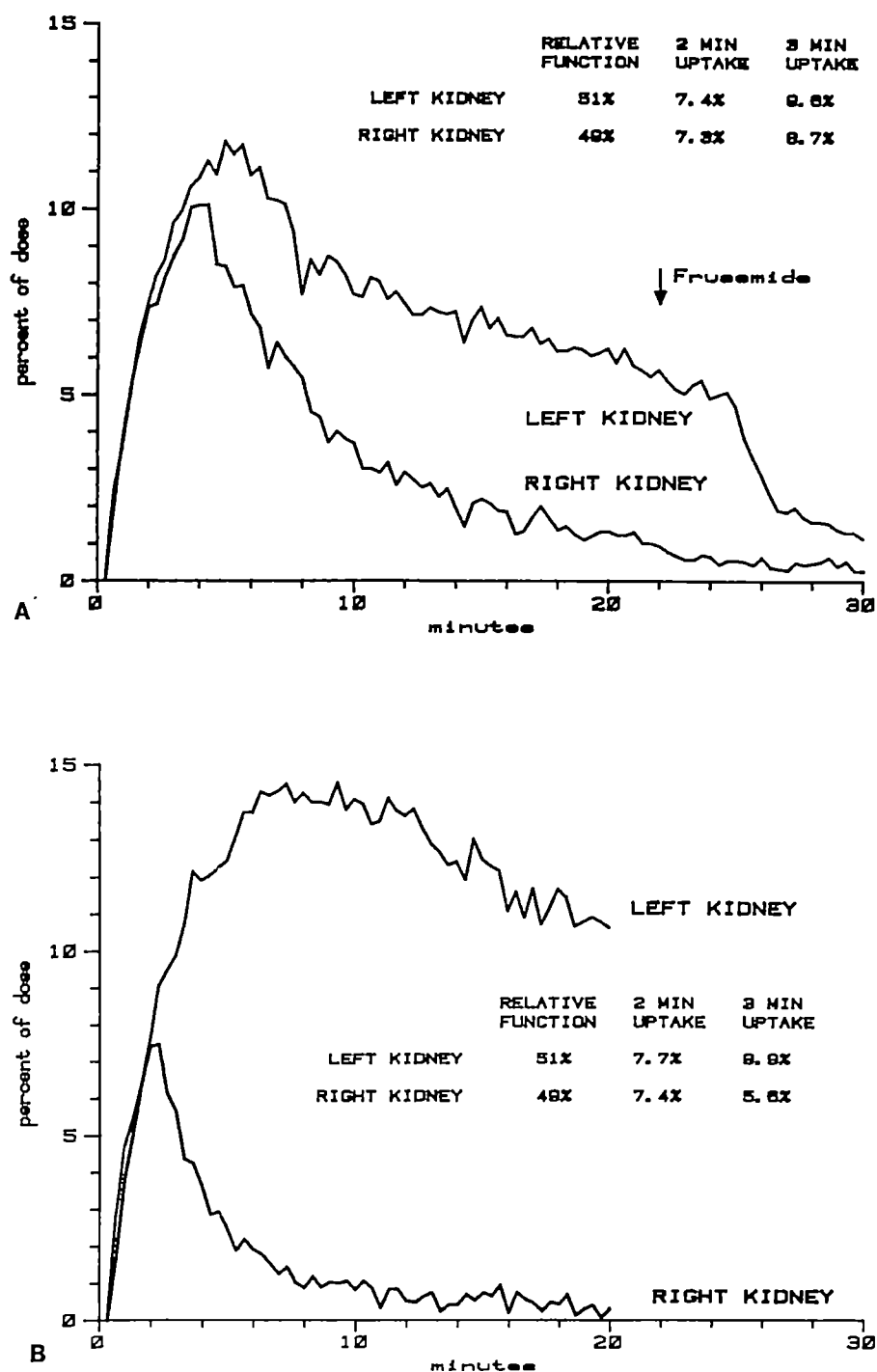


Fig. 1 (A) Standard diuresis renogram showing hypotonic washout from left kidney. (B) F-15 renogram in same patient showing obstructed left kidney at high urine flow rates.

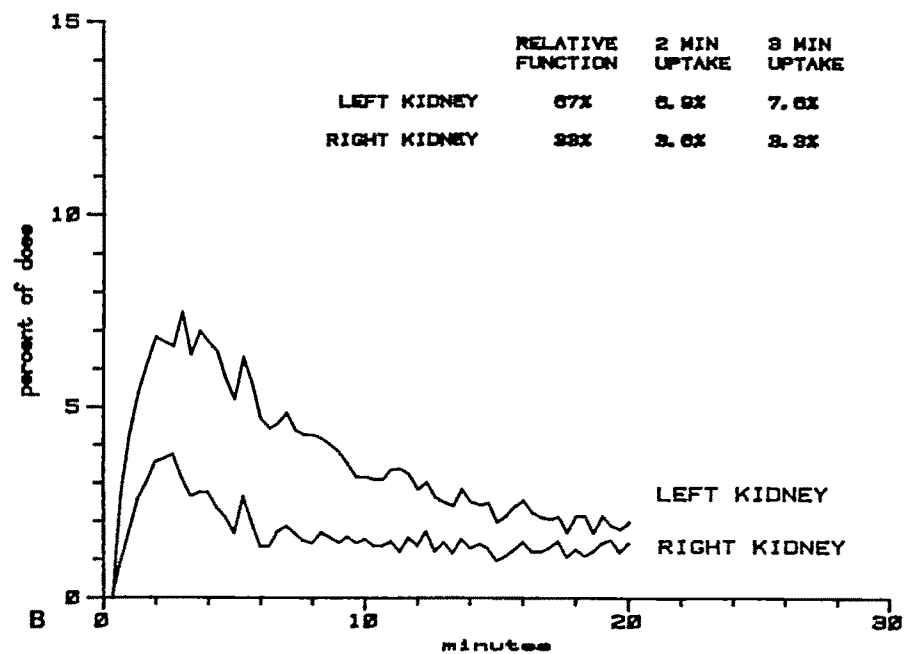
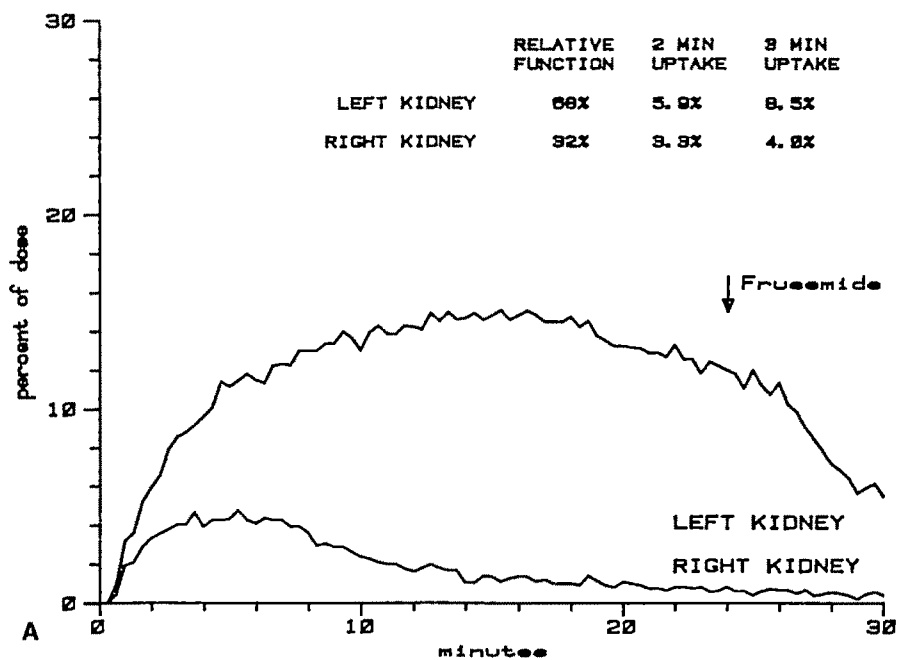


Fig. 2 (A) Standard diuresis renogram showing equivocal washout from left kidney. (B) F-15 renogram in same patient showing unobstructed left kidney.

and she therefore underwent further renal exploration at which no significant renal cause for her pain could be identified. The second patient who underwent pyeloplasty was more successful and showed symptomatic as well as renographic improvement following surgery.

Discussion

The diuresis renogram was introduced into clinical practice by O'Reilly in 1978. The purpose of the test is to distinguish between the dilated but unobstructed upper urinary tract and the truly obstructed kidney. In the majority of cases the standard diuresis renogram will do just that. However, in up to 17% of cases the results of diuresis renography will be equivocal (O'Reilly, 1987; Upsdell *et al.*, 1990) and the question "is the kidney significantly obstructed?" will not be answered. In an attempt to improve the accuracy of the diuresis renogram in the diagnosis of obstructive uropathy various modifications of technique or analysis have been introduced. Deconvolution analysis of the renogram with calculation of parenchymal transit time (PTT) is said to be a more sensitive indicator of obstruction than standard diuresis renography (Cosgriff and Berry, 1982; Britton *et al.*, 1987). However, other authors have demonstrated little advantage over standard diuresis renography (Lupton *et al.*, 1984) and the complexity of deconvolution analysis, the difficulties in analysing the renogram, particularly in children (Vivian *et al.*, 1985), and the availability of the simpler diuresis renogram have restricted the use of PTT in the investigation of dilated upper tracts.

Attempts to improve the diagnostic accuracy of the diuresis renogram by quantifying the response of the renogram curve have been made using a number of methods. The diuresis excretion index (DEI) was introduced by O'Reilly in 1978 for use with probe renograms and was later adapted to the gamma camera renogram (English *et al.*, 1987). Radionuclide clearance half times, which measure the time taken to clear half of the activity present in the kidneys after the injection of frusemide, have been calculated for obstructed and unobstructed kidneys (Maizels *et al.*, 1986). Unfortunately, both the DEI and clearance half times suffer from problems in defining the normal and obstructed ranges and both indices have a considerable range of equivocal results.

Modifications of the diuresis renogram which are

designed to increase urine flow rates during renography have been described by Sukhai *et al.* (1986) and English *et al.* (1987). The rationale behind these modifications is that the diuresis produced by standard diuresis renography may be insufficient to produce washout in grossly dilated systems (Zechman, 1988; Kletter and Nurnberger, 1989) or in kidneys with impaired renal function (O'Reilly, 1986; Hjortso *et al.*, 1988). This may result in an equivocal or even obstructed curve in the absence of true obstruction. Furthermore, a false negative result may be obtained in cases of intermittent pelviureteric obstruction that obstruct only at high urine flow rates (O'Reilly, 1989). We have demonstrated in other studies that diuretic-induced urinary flow rates reach a maximum 16 to 18 min after an intravenous injection of frusemide and that even at creatinine clearances as low as 40 ml/min the urine flow rates 15 min after frusemide are sufficient to produce unequivocal washout curves (Upsdell *et al.*, 1988; Brown *et al.*, 1992). The timing of frusemide in F-15 renography, 15 min before the injection of radiopharmaceutical, therefore results in maximal urinary flow rates occurring at the start of the renogram. This should ensure that the incidence of false positive results is minimised in grossly dilated or poorly functioning systems. In addition, the increase in urine flow rates may be sufficient to cause obstruction in those systems that obstruct only at high urine flow rates.

The results of the present study have shown that there was generally good agreement between standard renography and F-15 renography when the results of the standard renogram were unequivocal. However, it is of interest that 1 patient who demonstrated an unobstructed hypotonic pattern on standard diuresis renography was shown to be obstructed at high flow rate using modified renography, and subsequently required surgery. This patient presented with typical symptoms of intermittent pelviureteric obstruction with loin pain after alcohol consumption and represents one of the group of patients who obstruct only at high urine flow rate and who may not be identified by conventional radiographic or renographic investigations. In the vast majority of cases a non-obstructed result on standard diuresis renography will be a reliable assessment of upper tract drainage and management decisions can be taken without the need for modified renography. However, in those patients whose clinical presentation is strongly suggestive of upper tract obstruction, an F-15 renogram should be performed even in the presence of an unobstructed standard diuresis

renogram, to exclude high flow, intermittent, pelviureteric junction obstruction.

An obstructed F-15 renogram appears to be an indication for surgery, and all of the patients in this study who underwent reconstructive surgery on this basis showed both symptomatic and renographic improvement at follow-up.

All but 2 of the 39 patients with unobstructed F-15 renograms remained unobstructed on conservative management. One obstructed with an undiagnosed asymptomatic ureteric stone and the other underwent pyeloplasty 3 years after an unobstructed F-15 renogram without further renographic assessment; it is therefore difficult to comment on the significance of this case. There was no significant unexplained loss of relative function in this unobstructed group, and only 3 patients with persistent unexplained symptoms likely to be of renal origin. It would therefore appear safe to recommend conservative management in this group with unobstructed F-15 renograms.

Equivocal washout occurred in 23 of 55 cases using standard diuresis renography in this highly selective group with suspected obstruction of the upper urinary tract. F-15 renography clarified washout in 21 cases. An additional 2 cases of equivocal washout were revealed by F-15 renography, making a total of only 4 cases (7%) using this technique.

It was concluded that the F-15 renogram, in which frusemide is given 15 min before the test, appears to provide an accurate assessment of the drainage of the upper urinary tract. The incidence of equivocal results in the renographic assessment of suspected upper tract obstruction is significantly reduced by F-15 renography and this technique is recommended in either renographically or clinically equivocal cases.

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Effect of Percutaneous Nephrolithotomy on Thermoregulation

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Summary—Hypothermia is a well recognised complication of open surgery. We had observed hypothermia, occasionally followed by rebound hyperthermia in the early post-operative period, in patients undergoing percutaneous nephrolithotomy, and therefore decided to monitor patients undergoing this procedure more closely. During a 12-month period, 32 patients were monitored during 38 percutaneous nephrolithotomies; 12 procedures were performed using irrigation fluid at room temperature (22°C) and 26 with fluid warmed to 37°C. Although no statistically significant differences between temperature changes were seen, the most profound temperature falls occurred in patients who received fluid at room temperature. The recovery ward staff observed improved post-operative recovery in patients who had received warmed fluid. Three of the 5 patients who underwent more than 1 percutaneous procedure received fluid at 22°C and fluid at 37°C on separate occasions. In each patient a more profound temperature fall occurred when the cold fluid was used. Only 1 patient, who received cold fluid, developed rebound hyperthermia in the early post-operative period. Warming of irrigation fluid and close monitoring of core temperature may prevent unnecessary morbidity in patients undergoing percutaneous nephrolithotomy.

Hypothermia, defined as a core temperature below 36°C (Morley-Forster, 1986), results in a reduction in normal enzymatic and metabolic processes; ideally, internal body temperature should be kept at a value close to 37°C, the optimum for these processes (Imrie and Hall, 1990). Hypothermia results from an imbalance of heat loss and heat production, and it is a well recognised complication of surgery (Goldberg and Roe, 1966). These large fluctuations in body temperature could be due to alteration in hypothalamic thermoregulation. Having noticed that hypothermia seemed to be occurring in a high proportion of patients undergoing percutaneous nephrolithotomy (PCN), we decided to monitor carefully the core temperatures of patients undergoing PCN and to assess whether warming the irrigation fluid could reduce the risk of this complication.

Patients and Methods

Over a 12-month period, 32 patients (12 men and 20 women) undergoing 38 PCN procedures were monitored. Their mean age was 56 years (range 28–78); 24 of the 38 procedures were performed for staghorn calculus disease.

All patients received either opiate or benzodiazepine premedication. General anaesthesia was induced with intravenous propofol or thiopentone and maintained by ventilation via a closed circuit with nitrous oxide, oxygen and 1% enflurane. Intravenous atracurium or vecuronium were used as muscle relaxants. Anaesthesia was reversed by intravenous neostigmine and glycopyrolate.

The patient's core temperature was monitored using a tympanic temperature probe attached to a portable, battery-powered Hi-Lo temperature monitoring device (Mallinckrodt). The tympanic probe was inserted after induction of anaesthesia. The probe remained *in situ* for 24 h in all patients, and longer when indicated by the patient's clinical

condition. The core temperature display was monitored continuously and recorded in the patient's chart every 15 min until the core temperature returned to normal; thereafter it was recorded 4-hourly. For the purpose of this study, the lowest core temperature occurring within 2 h of surgery was used to define the peri-operative temperature change.

Cold fluid (22°C) was used for the first 12 procedures as no facility existed to warm fluid. As soon as a warming cabinet became available, the subsequent 26 procedures were performed with warm fluid (37°C). It was considered unethical to withhold warm fluid from patients when facilities were available to supply it, having observed profound hypothermia in some patients.

The normal saline used as irrigation fluid was warmed in a free-standing 80-L capacity Baird and Tatlock cabinet which had a solid state thermostat and accurately maintained a steady temperature of 37°C. It was found that the temperature of the irrigation fluid fell by 4°C/h and, in use, each 3-L bag ran through in approximately 10 min. In 30 procedures, the total volume of irrigation fluid used for each case was recorded, 10 of 12 procedures involving cold fluid and 20 of 26 procedures warm fluid.

Results

Temperature change

The temperature changes in patients receiving irrigation fluid at 22°C are shown in Figure 1. The temperature fell in 11 of the 12 patients receiving cold fluid, remaining unchanged in only 1. In patients receiving fluid at 37°C (Fig. 2), the temperature fell in 19 of the 26 patients, remained unchanged in 6 and rose in 1.

The relationship to irrigation volume

The temperature fall per litre in the 30 patients in whom the volume of fluid was recorded is shown in Figure 3. The volume of irrigation fluid used as a function of the length of the procedure can be seen in Figure 4.

Multiple procedures

Two patients underwent 3 separate debulking procedures, 1 receiving cold fluid on the first 2 occasions and warmed fluid for the 3rd, 1 receiving cold fluid for the first and warmed for the 2nd and 3rd. A further patient underwent 2 procedures: 1 with cold and a 2nd with warm fluid. The

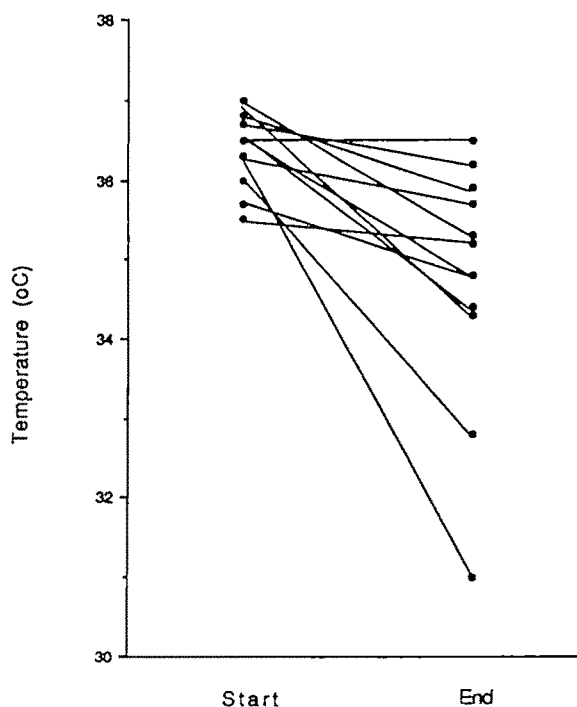


Fig. 1 Temperature change in patients undergoing percutaneous surgery with irrigation fluid at 22°C.

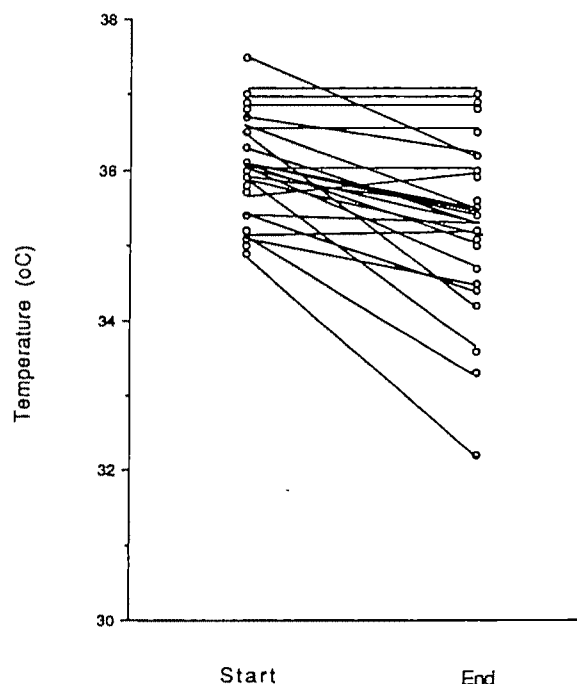


Fig. 2 Temperature change in patients undergoing percutaneous surgery with irrigation fluid at 37°C.

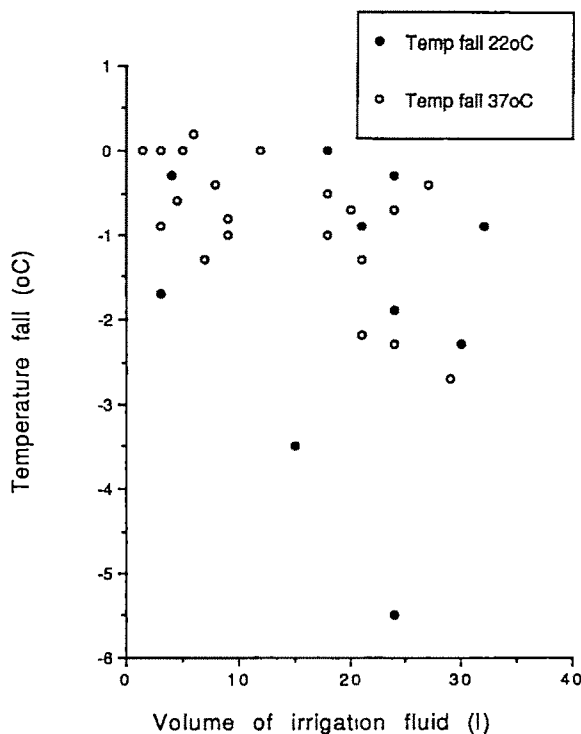


Fig. 3 Temperature change per litre of irrigation fluid used in patients undergoing percutaneous nephrolithotomy

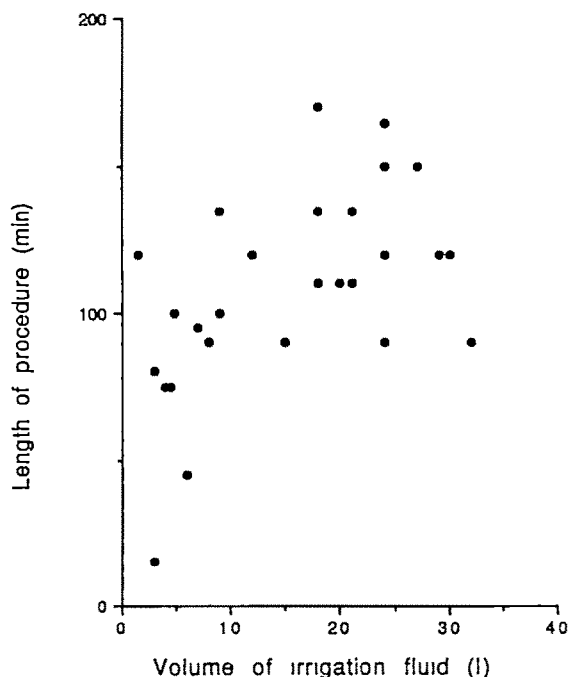


Fig. 4 Volume of fluid used for each procedure plotted against the length of time of the operation.

temperature fall was greatest when cold fluid was used despite the use of similar or larger volumes of fluid for the later procedure (Table). Two other patients received cold fluid for 2 procedures. The remaining patients underwent only 1 percutaneous procedure, receiving either cold or warm irrigation fluid.

Post-operative recovery

Post-operative hyperthermic response was observed in only 1 patient and this followed a procedure using cold irrigation fluid (Fig. 5). This patient's urine cultures before and after surgery were sterile and the procedure had been covered with prophylactic antibiotics. Several other patients developed minor pyrexial responses, some characteristic of sepsis, with both pre- and post-operative urine cultures confirming the presence of infection. The nursing staff in the recovery unit were questioned about the patient's recovery following percutaneous surgery, unaware of the temperature of the fluid used on each occasion. Their subjective response was that the patients who had received warm fluid recovered better than those receiving cold fluid.

Discussion

Fall in body temperature during surgery is well documented (Goldberg and Roe, 1966). The 3 major post-operative consequences associated with a fall in core temperature to between 33 and 36°C are shivering, peripheral vasoconstriction and delayed drug clearance (Morley-Forster, 1986). The shivering response is inhibited by general anaesthesia (Imrie and Hall, 1990), but this returns on recovery from the anaesthetic in order to generate heat, continuing until the core temperature is restored to normal. During shivering, oxygen consumption rises (Roe *et al.*, 1966), which may result in hypoxia. The vasoconstrictor response can cause haemodynamic instability as blood volume shifts gradually from the central compartment to the periphery on rewarming. If the temperature falls below 33°C, dysrhythmias, reduction in cardiac output and central nervous impairment may occur.

Tympanic thermometry has been reported as the most reliable method of measuring core temperature, and gives the best index of hypothalamic temperature (Benzinger, 1969). The greatest fall in core temperature occurs within 1 h of surgery and it is thus advisable that patients, particularly over the age of 65 years, should be monitored in the recovery room until core temperatures return to

Table Temperature Fall in Patients Undergoing more than 1 Percutaneous Procedure

Patient no.	Fluid temperature (°C)	Temperature change (°C)	Temperature fall (°C)	Volume of saline irrigant used (L)
1	22	36.7–34.8	1.9	24
	22	37.0–34.3	2.7	?
	37	35.9–35.2	0.7	24
2	22	36.3–32.8	3.5	15
	37	36.0–35.0	1.0	18
	37	36.5–34.2	2.3	24
3	22	36.5–31.0	5.5	24
	37	34.9–32.2	2.7	29

36°C. Although we used a conventional warming cabinet to store and warm all irrigation fluid prior to percutaneous surgery, microwave ovens have recently been reported to be a satisfactory method of warming fluid for transurethral resection (Stapleton *et al.*, 1990).

The majority of the factors resulting in heat loss can be avoided by simple means. These include maintaining an ambient theatre temperature of at least 22°C, avoiding volatile skin preparation agents, and using adhesive non-absorbent paper drapes rather than cotton drapes to prevent evapo-

orative heat loss. By warming the fluids used for intravenous infusion and operative irrigation, further heat loss by conduction may be prevented. Since renal blood flow is approximately 25% of cardiac output, the kidneys can act as excellent heat exchangers, and irrigating the collecting system with large volumes of cold fluid would be expected to cause considerable heat loss. To avoid the effect of renal heat exchange, it would appear logical to use warm fluid to irrigate the collecting system.

Having become aware of the problems resulting from hypothermia in a number of our patients, we commenced routine monitoring of temperatures in patients undergoing PCN, while arranging to obtain suitable facilities for warming the large quantities of fluid necessary for a long percutaneous procedure. Realising the potential problems associated with hypothermia, when facilities became available for warming the irrigation fluid we felt that it would be unethical to withhold warmed irrigation fluid, and were thus unable to perform a randomised comparison of fluid at 22°C and 37°C. This study records the impact of introducing warmed irrigation fluid into our practice. Although the nature of the study prevents strict statistical comparison, and many other factors will contribute to the final body temperature resulting from a percutaneous procedure, there seems little doubt that warming the irrigation fluid produces no demonstrable ill effects in patients undergoing PCN. Patients who received warmed irrigation fluid had fewer problems with thermoregulation than those who received irrigation fluid at 22°C.

Rebound hyperthermia was observed in only 1 patient studied, and this patient had received cold fluid. The lowest absolute temperature reached in this patient was 34.3°C, representing a fall of 2.7°C.

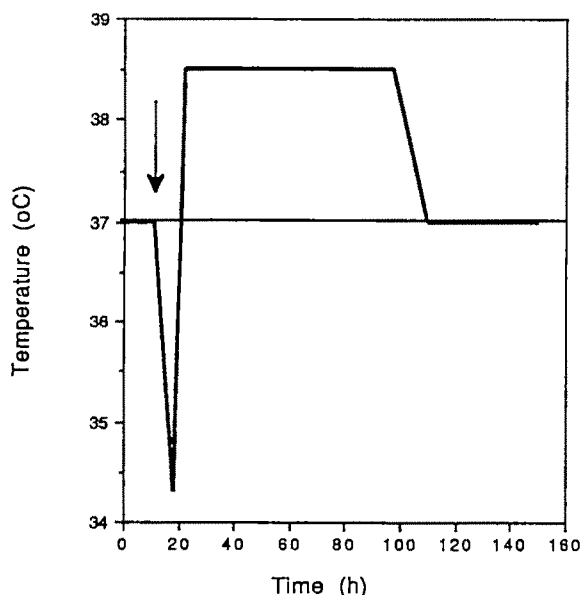


Fig. 5 Temperature chart of a patient following percutaneous nephrolithotomy, demonstrating rebound hyperthermia in the post-operative period. The arrow represents the time of percutaneous surgery.

Since this was not the lowest core temperature reached in either group, other factors such as the duration of hypothermia, prolonged bacteraemia or the presence of sepsis may influence the central control of thermoregulation (Judy, 1984).

Since avoiding hypothermia should reduce morbidity in patients undergoing percutaneous surgery, warming the irrigation fluid and close monitoring of core temperature seem to be sensible precautions.

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Initial Urethral Pressure Increase during Stress Episodes in Genuine Stress Incontinent Women

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Summary—The urethral and bladder pressure increments registered during a cough were investigated in 30 women with genuine stress incontinence (GSI) and compared with those from 30 previously investigated healthy women. The pressures were measured by means of a double microtip transducer catheter with the bladder sensor uncovered and the urethral sensor covered with a water-filled rubber cylinder and placed at the bladder neck, midurethrally, or distally in the urethra. In GSI women the pressure increment preceding the pressure spike produced by coughing was significantly higher in the bladder compared with the urethra, and the pressure increment seemed to be initiated in the bladder and all along the urethra simultaneously. In healthy women the pressure increment preceding a pressure spike was significantly higher in the midurethra compared with the bladder and it seemed to be initiated in the midurethra. These findings seem to reflect a defective active closure mechanism in GSI which may be a contributing factor in its pathogenesis.

The generation of a positive urethral closure pressure during stress episodes has been presumed to be a combination of passive pressure transmission from the abdominal cavity and active pressure generation (Enhörning, 1961; Constantinou and Govan, 1982; Caine, 1986). The differentiation *in vivo* of these closure pressures is difficult. However, during a stress episode, the early urethral pressure, taking place prior to the increase in bladder pressure, is believed to be solely active (Thind *et al.*, 1990).

This study was performed to measure the increments in bladder and urethral pressure preceding a pressure spike and to measure the time separation of the initiation of the 2 pressures during a stress episode in genuine stress incontinent women and to compare the results with previous measurements in healthy women.

Patients and Methods

Thirty women referred consecutively with GSI were studied. The age of the patients is shown in

Table 1. None had previously undergone surgery for incontinence. All had demonstrable urinary leakage at either a 1 or a 24 h pad weighing test (Jørgensen *et al.*, 1987; Lose *et al.*, 1988a) and all

Table 1 Ages, MUCP, FL and Maximum Pressure Increment Produced by Coughing in Healthy and Genuine Stress Incontinent Women

	Healthy volunteers (n=30)	Genuine stress incontinent (n=30)
Age (years)	42 (25–74)	49 (37–76)
MUCP (cmH ₂ O)	45 (37–55)	20 (15–34)
FL (mm)	33 (21–35)	32 (30–37)
P _{c ves} (cmH ₂ O)	64 (45–82)	76 (52–92)
P _{o ure} (cmH ₂ O)		
bladder neck	65 (43–83)	60 (43–71)
midurethra	73 (44–84)	49 (35–64)
distal urethra	39 (20–52)	35 (18–54)

Values are median with the range (age) or the 25th and 75th percentile in parentheses.

MUCP: Maximum urethral closure pressure.

FL: Functional profile length (measured with an 8F perfusion catheter).

P_{c ves}: maximum pressure elevation in bladder during cough.

P_{o ure}: maximum pressure elevation in urethra during cough.

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were without evidence of detrusor instability during medium-fill water cystometry.

The pressure measurements were performed using a specially designed double microtip transducer catheter (Lose *et al.*, 1986; 1988b). The tip sensor was placed in the bladder. The urethral sensor was covered with a 1.5 cm long, water-filled rubber balloon with a fixed cross-sectional area of 20 mm² (Thind *et al.*, 1990).

The women were examined in the supine position with an empty bladder. Urethral measurements were carried out at the bladder neck, in the high pressure zone and at the distal urethra (Thind *et al.*, 1990). The cough producing the greatest bladder pressure increase was used for calculation. Measurements obtained in healthy volunteers and in GSI women are shown in Figures 1 and 2. Informed consent was obtained from all of the women and the study was approved by the regional ethical committee.

Methods, definitions and units of measurements conform to the standards recommended by The International Continence Society except where specifically noted. The following definitions during a cough were used in this study:

P_1 : Pressure increase at the onset of pressure spike during cough.

t_1 : Time from the onset of pressure increase to the onset of pressure spike during cough.

Pressure spike: Pressure changes from the beginning of straight incline of bladder pressure

to the end of straight decline of bladder pressure during a cough.

The bladder and urethral pressures were registered, processed and displayed on a 6-channel recording system (Disa Urosystem 21 F 16 2100). The frequency response of the amplifying system was 100 Hz, paper speed 15 mm/s.

Statistical analysis was based on standard non-parametric methods using the Mann-Whitney test to analyse differences between 2 groups and the Wilcoxon or the Friedman test to analyse differences between 2 or more sites of measurement in the same group, respectively. $P < 0.05$ was considered statistically significant.

Results

The maximum pressure increases in the bladder and in the urethra during coughing are presented in Table 1. P_1 and t_1 are shown in Table 2. P_1 was statistically significantly greater in the bladder than all along the urethra. In a previously investigated group of healthy volunteers P_1 and t_1 were greater in the urethra than in the bladder.

During the cough episodes there was no time separation of the pressure spike between the bladder and urethra.

Discussion

This study has demonstrated that the pressure

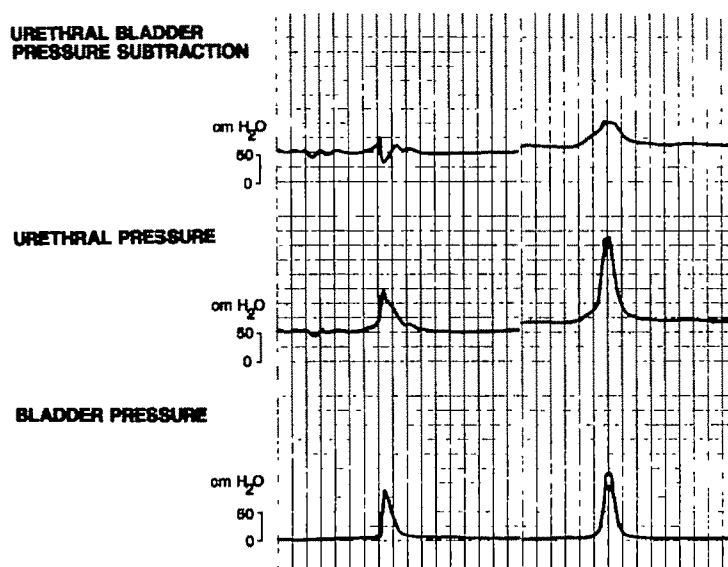


Fig. 1 Urethral and bladder pressure measurement in the high pressure zone during a cough in 2 healthy women

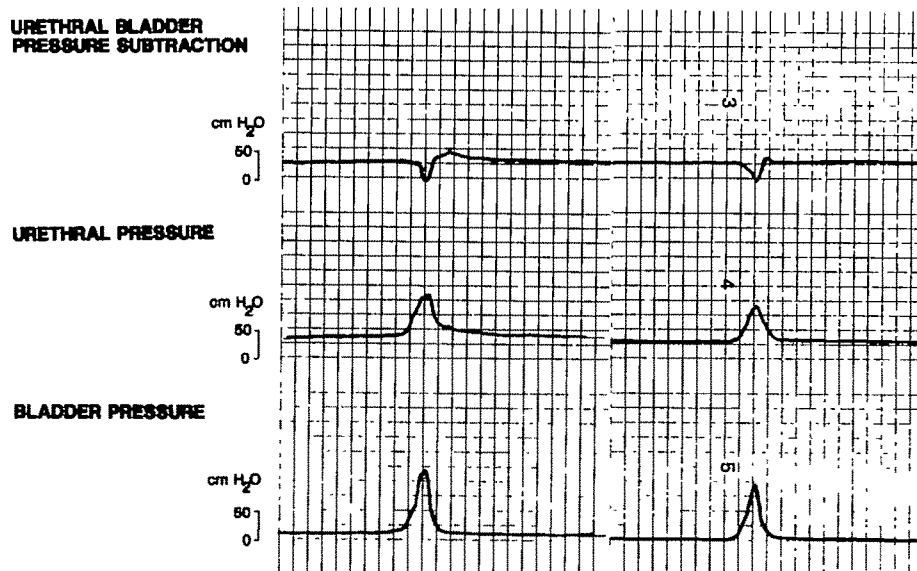


Fig. 2 Urethral and bladder pressure measurement in the high pressure zone during a cough in 2 GSI women.

Table 2 P_1 and t_1 Measured in 30 GSI Women

	Site of measurement			
	Bladder	Bladder neck	Midurethra	Distal urethra
P_1 (cmH ₂ O)	20 (11–32)* 22 (17–26)** 20 (13–30)**	15 (13–24)*	13 (7–25)**	10 (10–24)**
t_1 (ms)	200 (140–290) 300 (145–300) 300 (120–450)	250 (200–300)	300 (200–490)	300 (200–500)

* $P < 0.05$ ** $P < 0.01$

Values are median with the 25th and 75th percentile in parentheses

increment preceding the pressure spike during a cough is statistically significantly greater in the bladder than the corresponding pressure increase along the urethra in GSI women. The pressure increase was initiated simultaneously in the bladder and urethra. In healthy volunteers P_1 has been found to be statistically significantly higher in the midurethra than in the bladder and, furthermore, the pressure increase was initiated in the midurethra followed by the bladder neck and then the bladder (Thind *et al.*, 1990). Interpretations of differences of pressures or time separations during stress episodes between healthy and GSI women should be made very cautiously as the stress episodes may not be of identical magnitude. However, the

influence of the effort of the stress episode is probably reduced when comparing bladder and urethral pressure measurements in the same subjects. In this study the increment of bladder pressure during cough was higher in GSI women than in healthy women.

The results in this study show that the urethral pressure increment preceding a pressure spike is reduced and delayed in GSI women in comparison with healthy women. This observation indicates that active mechanisms affecting the midurethra are defective or weakened in GSI women, which may be of pathogenic importance. The findings accord with recent electrophysiological evidence (Smith *et al.*, 1989).

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Role of the Artificial Urinary Sphincter in the Treatment of Stress Incontinence in Women

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Summary—The artificial urinary sphincter (AUS) is rarely indicated in the treatment of women with stress incontinence because most of these women have deficient urethral support rather than pure sphincter weakness and the AUS is a treatment specifically for pure sphincter weakness. The procedure is contraindicated after pelvic radiotherapy and after previous sling surgery because of the high incidence of cuff erosion. Otherwise the artificial sphincter gives excellent results comparable to those seen in men with post-protatectomy incontinence and much better than in neuropathic bladder dysfunction.

Most women with genuine stress incontinence are satisfactorily treated by a Burch-type colposuspension or a Stamey-type of bladder neck suspension or one of the numerous variations of either theme. Unfortunately, incontinence recurs in up to 30% of patients after 5 years (Park and Miller, 1988; Wheelahan, 1990), resulting in further surgery. These secondary procedures often prove unsatisfactory and the incontinence persists. Since the introduction of an effective and reliable artificial urinary sphincter it has become common for such patients to be considered for implantation of such a device.

This report describes our experience in such patients.

Patients and Methods

In the last 9 years, 119 women with stress incontinence that had failed to respond to standard anti-incontinence surgery using either a Burch-type or a Stamey-type procedure were referred to this hospital for implantation of an AUS. All patients had undergone at least 2 previous operations and

78 patients had had 3 or more operations, not including an anterior colporrhaphy. In 5 patients a urethral sling was inserted and 7 had a radical course of external beam radiotherapy to the pelvis. All patients had videourodynamic studies performed by the referring urologist or gynaecologist and the majority had been shown to have stable bladders, but 26 instances of detrusor instability were detected when repeat urodynamic studies were performed in this laboratory. Seven women were unfit for surgery when assessed by the anaesthetist and 2 did not want any further surgery.

Of the remaining 84 patients (mean age 47 years, range 29–74), physical examination and/or the video appearances on urodynamics showed a moderate to severe loss of urethral support in 63, together with a variable degree of sphincter weakness. In the remaining 21 women the problem seemed to be pure sphincter weakness. Nine of the women with overt loss of urethral support were treated by a Stamey-type transvaginal bladder neck suspension procedure. The other 75 women underwent open exploration of the pelvis with a view to implantation of an AUS, but in only 29 patients was an AUS actually implanted and in 4 of these only the cuff was implanted. In the other 46 patients a healthy bladder neck and proximal urethra were found once the scar tissue immediately deep to the previous incision(s) and over the anterior bladder

wall had been divided. It was therefore possible to do an adequate mobilisation of the bladder neck and urethra and perform a Burch-type colposuspension with relative ease.

Results

All 9 patients treated by a Stamey-type procedure were improved, with 8 of them becoming subjectively and objectively continent. One patient remained slightly "damp".

Of the 46 women treated by exploration of the retropubic space, division of adhesions and colposuspension, 39 (85%) were subjectively cured or sufficiently improved for them to be happy with the result. On objective evaluation 35 of these patients (76%) were cured. One of the 7 patients with persistent symptoms following colposuspension was subsequently improved by a Stamey-type procedure. No patient in this group subsequently required an AUS.

Of the 29 patients in whom an AUS was implanted, 5 had previously failed to respond to sling surgery and a radical course of pelvic radiotherapy had been unsuccessful in 7. In 8 of these 12 patients the cuff eroded and had to be removed. In no case could the erosion be attributed to surgical trauma at the time of the implantation. The other 4 patients had a satisfactory result.

Fifteen of the remaining 17 patients had a satisfactory result, 1 required 2 revisions for sphincter-related problems and another developed an infection requiring removal of the device. In this patient and in the 8 patients with cuff erosion in the radiotherapy/sling group, further treatment was either a neo-urethroplasty or a continent diversion with a Mitroffanoff-type procedure.

Discussion

Patients who have failed to respond to stress incontinence surgery are often difficult to treat. However, our findings confirm that in the majority of these patients an AUS is not indicated. A thorough physical examination and videourodynamic assessment are essential in this group of patients to define the exact cause of the incontinence and specifically to exclude detrusor instability.

If genuine stress incontinence is confirmed, it is important to determine whether the problem is mainly due to poor bladder neck and urethral support or to true sphincter weakness, which is typically demonstrated by an incompetent bladder neck and proximal urethra but a well supported

bladder base in the absence of a detrusor contraction on videourodynamic investigation. Urethral pressure profilometry may help in the diagnosis of sphincter weakness but its diagnostic capabilities are limited (Versi, 1990).

In most of our patients the problem was inadequate bladder neck and proximal urethral support. Undoubtedly there is an element of sphincter weakness in many, if not all, but it is the loss of support that seems to be the important factor. These patients are best treated with further bladder neck suspension surgery. If there is gross mobility of the bladder base on either physical examination or videourodynamics, indicating that there is little if any support at all, then this can be achieved with any bladder neck suspension procedure, but a Stamey-type operation is the easiest and the least traumatic to the patient.

If there is limited mobility indicating that there is some support, but support that is quantitatively or qualitatively inadequate, we have found that the best results are obtained by a suprapubic approach to divide the perivesical and periurethral scar tissue and so free up the bladder and urethra to do a Burch-type colposuspension. With this approach satisfactory results were achieved in 85% of patients and we believe that freeing up the scarring of previous retropubic operations plays an important part in obtaining a satisfactory result.

An AUS is therefore only indicated in pure sphincter weakness with no loss of urethral support. Even then some of these patients may benefit from suspension surgery either because the loss of support is subtle or because the procedure produces its effect by being obstructive. Alternative options include bladder neck reconstruction, a urethral sling or periurethral injection of Teflon or collagen or an artificial urinary sphincter. We prefer the AUS because the other options carry a high risk of complications and some are of unproven value; in addition, if these procedures fail, any subsequent surgery is made very much more difficult.

Our results indicate that the AUS, when indicated, provides satisfactory results and is well tolerated. Complications were few if the patients with previous pelvic radiotherapy or sling surgery are excluded, as they had an unacceptably high complication rate, with a cuff erosion rate of 67%. These patients are no longer considered for an AUS but are treated with either a neo-urethroplasty, using a bladder flap technique if they have had a sling procedure, or by either a substitution cystoplasty or a continent diversion if they have had previous radiotherapy.

Problems in sphincter implantation are invariably due to difficulties in developing a plane of dissection between the urethra and bladder neck anteriorly and the vagina posteriorly. This dissection is undoubtedly helped by vaginal manipulation. The use of a transurethral resection steri-drape permits repeated vaginal manipulation without the need to change gloves, minimising contamination of the suprapubic wound with vaginal organisms. If there is still difficulty, opening the bladder to see and feel the bladder neck area from inside often helps. If problems are still encountered, the bladder base should be separated from the anterior vaginal wall transperitoneally down to the bladder neck level and just below the ureteric orifices as for a hysterectomy. It is then easy to dissect through under the ureter to the retropubic space on either side and thus create a plane from one side of the retropubic space to the other in which the cuff can sit.

Experience with the AUS shows that the incidence of complications is low in post-prostatectomy incontinence and high in neuropathic bladder dysfunction (Mundy, 1991). The results in women with stress incontinence are almost as satisfactory as in men with post-prostatectomy incontinence,

despite the much more difficult dissection required, provided patients with previous radiotherapy or sling surgery are excluded. Thus, although the AUS is only rarely required, when it is used the results are very satisfactory.

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Pyuria: Index of Infection in Patients with Spinal Cord Injuries*

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Summary—Little is known about the significance of pyuria in patients with spinal cord injuries. The progress in hospital of 55 such patients was studied. They were divided into 2 groups according to the method of bladder drainage on admission. Group A comprised 43 patients with indwelling catheters. Group B comprised 12 patients who were able to void with tapping, with/without compression and on intermittent catheterisation.

The results showed that group A had a mean pyuria level of 185 WBC/HPF on admission. The incidence of urinary tract infection was 4 per patient during hospitalisation and the mean duration of bladder training was 82 days. Group B had a mean pyuria level of 32 WBC/HPF on admission. The incidence of urinary tract infection was 1 per patient during hospitalisation and the mean duration of bladder training was 40 days. The difference between groups A and B for all 3 parameters was statistically significant.

These results suggest that patients with spinal cord injuries and indwelling catheters have a higher pyuria level and an increased risk of significant morbidity secondary to urinary tract infection, especially at the pyuria level of 100 WBC/HPF. A low pyuria level of ≤ 30 WBC/HPF was associated with a nil or low incidence of bacteriuria and urinary tract infection in our patients.

Loss of normal bladder function results in an increased risk of developing urinary tract infection. Recurrent pyuria and bacteriuria continue to be a problem in most patients with spinal cord injuries.

Indwelling urethral catheterisation is the most frequent form of bladder drainage used in patients with neurogenic bladder dysfunction secondary to spinal cord injury (SCI), acute systemic illnesses, strokes, neurological and rheumatological diseases and head injury patients, especially in the acute phase. Indwelling urethral catheters contribute to the development of significant bacteriuria and are responsible for the high incidence of urological complications that include lower and upper urinary tract infections, vesicoureteric reflux, urinary tract

stones, periurethral inflammation, abscesses and possible septicaemia (Kyle, 1968; Warren *et al.*, 1981).

Pyuria is often found in association with urinary tract infection (UTI) and quantitative estimates are often used by clinicians to help in the diagnostic evaluation of urinary tract infection and the significance of bacteriuria in asymptomatic patients. Stamm (1983) suggested that in the absence of symptoms, pyuria was one means of distinguishing urinary tract invasion from bacterial colonisation of the bladder. Anderson and Hsieh-Ma (1983), noting that many spinal cord injury patients with pyuria were asymptomatic, stated that the level of pyuria should be evaluated to determine the degree of urinary tract invasion.

Since pyuria is one index of urinary tissue inflammation, we postulated that SCI patients with indwelling catheters and high levels of pyuria were more likely to develop recurrent urinary tract infection, fever and other urological complications.

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The progress in hospital of 55 SCI patients was therefore studied to determine whether such a relationship existed.

Patients and Methods

We studied the progress in hospital of all SCI patients admitted to this department between August 1989 and August 1990. The patients were divided into 2 groups, based on the method of bladder drainage upon admission. Patients were excluded from the study if:

- (1) Urine cultures grew <100,000 colony forming units/ml.
- (2) >100,000 *Candida* species were present in the urine culture.
- (3) They were on antibiotics at the time of admission.
- (4) They were febrile on admission.
- (5) Nephrolithiasis was present.
- (6) Genital infections, including vaginitis, were present.
- (7) Grades III or IV pressure sores were present.
- (8) Systemic infection was present.

Urine analysis and culture were done twice a week in order to determine the level of pyuria on admission and during their stay in hospital, and the incidence of pyuria and bacteriuria was then correlated.

Statistical Analysis

Data were obtained from case records and urology charts and the age, sex, level of spinal injury, level of pyuria on admission, pyuria during episodes of urinary tract infection and relevant bacterial urinary cultures were included (Table). These observations were carried out while patients were on indwelling catheters or on intermittent catheterisation.

Student's *t* test was used to determine the significance of the differences between Groups A and B in relation to pyuria on admission, the incidence of urinary tract infection and the duration of bladder training.

Results

None of the patients developed any other significant systemic infection during the study. All responded to a combination of oral or intravenous antibiotics and regular bladder washouts. Only 2 patients went home or to institutional care with indwelling catheters. Of the remaining 53 patients, 45 could void with/without tapping and compression after a period of bladder training; 8 patients could not be bladder trained and went home on a regime of clean intermittent self-catheterisation.

Statistical analysis of the data showed that:

- (1) The difference in the pyuria level on admission for Group A and Group B was statistically significant ($t=2.078$, $P<0.05$).
- (2) The difference in the incidence of urinary tract infection for Group A and Group B was significant ($t=2.047$, $P<0.05$).
- (3) The difference in the duration of bladder training between Group A and Group B was significant ($t=2.175$, $P<0.05$).

Discussion

Most clinicians agree that asymptomatic bacteriuria should not be treated in chronically catheterised patients because routine treatment encourages the emergence of resistant organisms (Merritt, 1976; Kunin, 1987).

The classical symptoms of urinary tract infection (dysuria, frequency, urgency and suprapubic pain) are unreliable and usually absent in SCI patients

Table Details of Patients

	<i>Method of bladder drainage</i>	
	<i>Indwelling catheter (Group A)</i>	<i>Intermittent catheterisation (Group B)</i>
No. of patients	43	12
Mean age (years)	35	43
Mean pyuria rate on admission (WBC/HPF)	185	32
Mean pyuria rate during febrile state or on starting antibiotics (WBC/HPF)	155	115
Mean incidence of UTI/patient/hospitalisation	4	1
Mean duration of bladder training (days)	82	40
Mean duration of stay in Rehabilitation Department (days)	114	60

with neurogenic bladders and impaired sensation. Most lower urinary tract infections are asymptomatic in this population (Merritt, 1976). Clinicians usually wait until objective criteria such as fever are present to determine which patients should receive antibiotic therapy. However, by the time fever is present in SCI patients, the upper urinary tract may be involved.

Pyuria is an index of tissue inflammation. Its absence indicates that no urinary tract infection is present; its presence helps to distinguish between colonisation and true infection of the urinary tract (Stamm, 1983; Hooton *et al.*, 1984). However, the measurement of pyuria by microscopic examination is poorly reproducible because of observer bias, technician error, lack of standardisation of the thickness of the film and varying volumes of resuspension (Gadeholt, 1964; Gribble *et al.*, 1988).

This study supports the claim that spinal cord injury patients with indwelling catheters have a higher pyuria level than those without. This predisposes them to an increased incidence of urinary tract infections, leading to significant morbidity. Patients with a pyuria level >100 WBC/HPF developed a urinary tract infection, had associated bacteriuria and required antibiotic treatment. There was also a higher incidence of urinary tract infection in this group of patients. A low pyuria level of 30 WBC/HPF was generally found in SCI patients without indwelling catheters and they showed a significantly lower incidence of urinary tract infection. It is also important to note that the duration of bladder training was significantly shorter in Group B patients, who had a low pyuria level (≤ 30 WBC/HPF), compared with Group A patients with a high pyuria level (>100 WBC/HPF).

We conclude that if clinicians wish to reduce the risk of urinary infection in patients with neurogenic bladder, indwelling catheters must be removed as soon as possible. The pyuria level should be monitored because a low pyuria level (≤ 30 WBC/HPF) was normally associated with a nil or low incidence of urinary tract infection in our patients. A consistently raised pyuria level (30–100 WBC/HPF) should be treated with bladder washouts with/without oral antibiotics if bacteriuria is associated with the pyuria. A high pyuria level (>100 WBC/HPF) in this study was always associated with bacteriuria and systemic symptoms and required oral or intravenous antibiotics.

The use of pyuria as an index of infection has helped us to treat urinary tract infection in SCI patients, who do not usually have classical symptoms of infection. If urinary tract infection is treated early and adequately, morbidity can be reduced, as can the incidence of urological complications. This enables patients to go home sooner and helps them to live a more meaningful life with better and longer preservation of renal function, the ultimate goal of any method of neurogenic bladder management.

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Intravesical BCG Treatment for Superficial Bladder Cancer: Long-term Results using Two Different Strains of BCG

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Summary—A total of 21 patients received intravesical BCG for the prevention of recurrence of superficial transitional cell carcinoma of the bladder. Twelve patients received the Glaxo strain and 9 the Pasteur strain of the bacillus. Although thought to have different anti-tumour activities owing to a difference in antigenicity, these 2 strains produced similar tumour-free rates at 5 years' mean follow-up with an overall tumour-free rate of 43%.

The use of BCG (Bacille Calmette-Guérin) to treat malignancy in humans was first reported by Holmgren in 1935. The modern use of BCG in cancer therapy began with Mathe *et al.* in 1969 when they demonstrated the efficacy of the bacillus in the treatment of acute leukaemia in children. The application of BCG to the management of bladder cancer was initiated by Morales *et al.* (1976). In the ensuing 2 decades numerous reports have followed, and BCG has come to be recognised as an effective biological agent in the treatment and prophylaxis of superficial bladder cancer. The American Medical Association Panel on diagnostic and therapeutic technology assessment (DATTA) in 1988 determined that BCG immunotherapy is both safe and effective for application in superficial bladder cancer.

BCG has been used more extensively in North America than in the United Kingdom and this may be because results using the strains available in the UK have been less encouraging (Robinson *et al.*, 1980). Morales (1984) and Lagrange *et al.* (1976) suggested that the Glaxo strain of BCG commonly used in the UK is a compound of poor antigenicity compared with the Pasteur and Tice strains which are commonly used in North America. Reservations

have also been expressed regarding the long-term effectiveness and potential complications of intravesical BCG therapy. We have reviewed the long-term results of a trial comparing the effectiveness of Pasteur and Glaxo strains of BCG vaccine in the prophylaxis of superficial bladder cancer.

Patients and Methods

This trial was initiated in 1984 and included 21 patients with multiple recurrent superficial bladder tumours that were increasingly difficult to keep under endoscopic control; 17 patients were male and 4 were female. Five patients had received prior intravesical instillation of Epodyl or doxorubicin without significant benefit. In 13 cases the tumour was histologically average grade (G2), in 2 cases it was high grade (G3) and in 4 cases it was low grade. In 2 cases there was extensive carcinoma *in situ* within the bladder with no associated overt tumours. All tumours were superficial (pT1 or less). Patients were randomised to receive either the Glaxo (n = 12) or the Pasteur (n = 9) strain of BCG vaccine. Via a urinary catheter the vaccine was instilled diluted in 100 ml normal saline, this dose of BCG containing 1.2×10^9 colony-forming units. Each initial instillation was carried out within 10 days of endoscopic resection or fulguration of all visible bladder tumour. This was done because (theoretically) a disrupted urothelium facilitates

maximal localisation of bacterial antigens. The retention time of the vaccine solution within the bladder was 1 h, following which the patient was allowed to void. Whilst the solution was in the bladder the patient was made to turn at 15-min intervals so that anterior, posterior and lateral walls were equally "coated" with the vaccine suspension. An intradermal dose of BCG was also administered at the first instillation. Six weekly instillations were given followed by a review cystoscopy 3 months after the first instillation. Further BCG instillations were given depending on the response seen at the first cystoscopy after treatment. Patients received either monthly instillations if there was a complete response or a further 6-week course of treatment if there was a partial or no response. A complete response was defined as no tumour recurrence together with negative bladder biopsies and negative urinary cytology. A lack of response to treatment or disease progression were regarded as therapeutic failures. Subsequent cystoscopic follow-up was carried out within 3 months of the final instillation and further cystoscopies performed according to clinical criteria. The analysis of results of therapy was undertaken at a mean follow-up time of 60 months.

Results

A single 6-week course of BCG was administered to 16 patients (9 in the Glaxo and 7 in the Pasteur group). Ten of these patients underwent further monthly instillations ranging from 4 to 15 in number. Four patients underwent 2 six-week courses and 1 received 4 six-week courses. Four of these 5 patients subsequently had between 3 and 6 monthly instillations each.

The 1-year follow-up of these patients revealed a complete response rate of 64% for the Glaxo and 56% for the Pasteur group (Kaisary, 1987). At 5 years' mean follow-up (range 38–72 months), 9 of 21 patients were free of tumour and thus judged to be complete responders (Table). This group constituted 5 patients from the Glaxo group and 4 from the Pasteur group, a difference that was not statistically significant. All 9 responders were patients with average/low grade disease who have remained tumour-free under annual endoscopic review. Another patient who was a responder at 12 months had to be excluded from further follow-up because of severe myocardial disease.

The review of treatment failures is interesting. Two patients receiving the Glaxo strain who exhibited no early response (1 with average grade

Table Results of BCG Instillation at 1 and 5 Years' Follow-up

	<i>Pasteur</i> (<i>n</i> =9)	<i>Glaxo</i> (<i>n</i> =12)
At 1 year		
Complete response	5	7
Failures	4	5
At 5 years		
Complete response	4	5
Failures	5	7

tumour and 1 with carcinoma *in situ*) underwent subsequent cystectomy for progression of disease. Both are alive and well at follow-up. Four patients (all with average/low grade disease) remain under endoscopic control with follow-up ranging from 44 to 72 months. One of these is a patient who, after initial consideration for cystectomy, continues to have an average of only 3 recurrences at each review cystoscopy 44 months later. These 4 patients (3 from the Glaxo and 1 from the Pasteur group) may be classified as partial responders according to standard EORTC recurrence criteria (Sylvester, 1985). Five patients have died from bladder carcinoma during the period of this study. One patient had carcinoma *in situ* and 2 others had high grade tumour which never responded. Two patients had bladders which were completely free of tumour at their most recent cystoscopy but both had widespread metastases, one of which was associated with invasive urethral recurrence. Overall, at 5-year follow-up the group treated with the Pasteur strain of BCG was 1.12 times more likely to be free of disease than was the Glaxo group, but this difference was not statistically significant (the 95% confidence intervals for this ratio being 0.18–6.7).

Treatment with BCG was generally well tolerated for both strains of the vaccine but most patients did complain of haematuria and dysuria. This was transient, lasting 2 to 3 days on average, and rarely distressing. Another disadvantage of this treatment regime was the relatively high frequency of urethral catheterisation required. Local reactions to intradermal BCG were severe on occasions and this practice has been discontinued since this trial was completed. No pyrexia or systemic reactions were observed in this series.

Discussion

The effectiveness of bacillus Calmette-Guérin in the prophylaxis and treatment of superficial bladder cancer has been demonstrated repeatedly with

clinicians reporting remission rates of 51 to 94% (Brosman, 1982; Kaisary, 1987). The main difficulties in comparing the results of trials evaluating the role of intravesical BCG have been (1) the use of differing strains of the bacillus with varying antigenic properties and (2) the use of varying treatment regimes. Our results gave a complete response in 43% of patients overall for both strains of BCG. These results compare favourably with the results of Morales (1984), who had a tumour-free rate of 48% at a mean follow-up in excess of 5 years using the Frappier bacillus but unfavourably with other series; Brosman (1985) reported a tumour-free rate of 82% (mean follow-up 5.2 years) and Herr *et al.* (1986) reported a tumour-free rate of 65% (mean follow-up 51 months). The reasons for these different response rates may lie not only in the use of strains with differing antigenic properties but also in the selection of patients and the employment of different regimes. We have shown in this small series that there is no significant difference in response rates obtained at long-term follow-up between patients who received the Glaxo bacillus and those who received the Pasteur bacillus (42% versus 44% respectively) (Fig.). It is important to note, however, that in the current series the numbers were too small to enable us to stratify response according to grade and stage in a satisfactory statistical manner. It is now generally held that patients with superficial bladder cancer who respond to BCG often remain free of tumour and progression of disease for 5 years or longer (Herr, 1989).

The most effective protocol for BCG administra-

tion has not yet been defined, nor has the role of maintenance intravesical therapy. Hudson *et al.* (1987) and Badalment *et al.* (1987) found no difference in tumour recurrence rates between patients receiving the initial 6-week course of instillations and those who in addition received maintenance therapy. Lamm (1985) and Brosman (1982), however, reported better results with repeated intravesical BCG instillations for periods of between 1 and 2 years. Theoretically, maintenance therapy is supposed to maintain or reactivate the anti-tumour response locally to prevent bladder tumour recurrence. We have treated or are treating another 18 patients with the Pasteur strain of bacillus, administering maintenance therapy at monthly intervals following the initial 6-week course. That the anti-tumour effect of BCG is probably local only is exemplified by the fact that 2 of our patients had bladders free of tumour at review cystoscopy but had developed widespread extravesical disease.

Serious side effects have not been seen in this series or in our subsequent experience with intravesical BCG instillation, although serious complications have been reported by other investigators (Lamm *et al.*, 1989). Granulomatous prostatitis, renal granulomata, ureteric obstruction and BCG septicaemia have all been reported and this emphasises the need for careful catheterisation and administration of the vaccine. Complications relating to the dermal administration of the vaccine prior to treatment may now be avoided, as recent evidence suggests that this is not a necessary adjunct to treatment (Lamm *et al.*, 1991). Intraves-

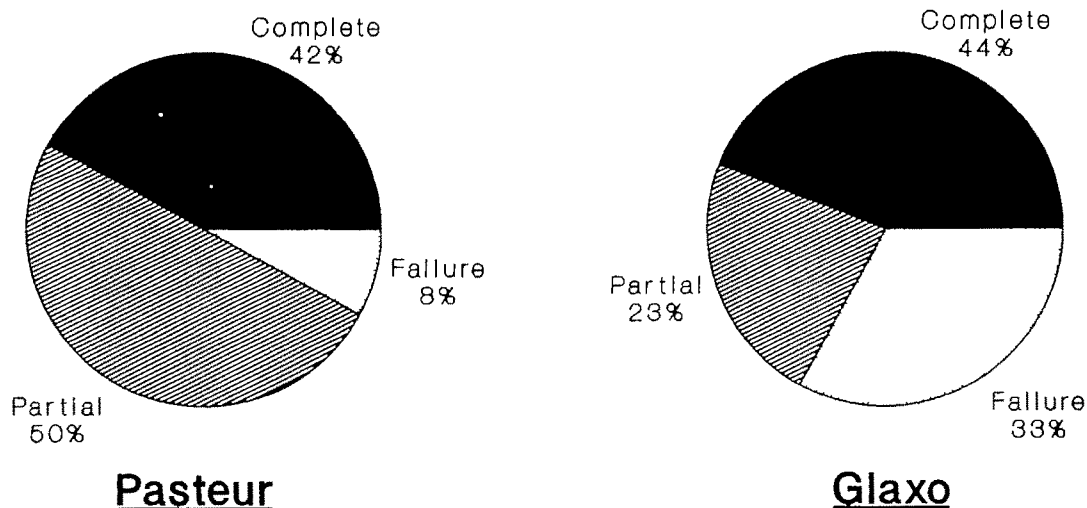


Fig. Response to intravesical BCG at 5-year follow-up.

ical BCG is an effective and safe treatment modality for the prevention of tumour recurrences in superficial transitional cell carcinoma of the bladder. However, much remains to be learned about the mechanism of its action and its optimum regime of administration.

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Bladder Cancer: Inter-relationships between Chemotherapy and Radiotherapy

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Summary—There has been increasing interest in the role of chemotherapy as primary treatments for patients with urothelial cancer and because of the poor prognosis of locally advanced tumours with conventional treatment, trials have been initiated comparing radiotherapy with chemotherapy as primary therapies. In this context it is important to assess the relationship between the responses to chemotherapy and radiotherapy, and this we have examined in 64 patients treated with MVMJ (methotrexate, vinblastine, mitozantrone and carboplatin).

Either a complete or a partial response was found in 29 of the 64 patients, 15 had stable disease and 13 had progression of disease. Seven patients died within the first treatment month. The survival of the responding patients ranged from 114 to 1184 days.

Six of 15 patients who had had pelvic irradiation prior to chemotherapy responded to MVMJ, the maximum duration of response being more than 3 years.

Twenty-two patients had radiotherapy following their chemotherapy. One of 13 patients not responding to MVMJ had a transient response to radical radiotherapy. Only 1 of 9 patients responding to chemotherapy and then relapsing responded to subsequent radical radiotherapy.

Patients with metastatic disease or with recurrent disease after radiotherapy have a worthwhile chance of responding to chemotherapy and achieve durable remissions. In contrast, radiotherapy appears relatively ineffective in patients whose disease progresses or relapses after chemotherapy given as primary treatment with curative intent.

The prognosis of locally advanced or metastatic urothelial cancer is poor: 5 to 10% of patients with T4 tumours survive 5 years and 5% of those with metastatic disease survive 1 year (Quilty *et al.*, 1986). In an attempt to improve upon this appalling outlook, combination chemotherapy programmes which have been shown to be relatively successful in the management of patients with metastatic urothelial tumours have been applied to patients with locally advanced disease, as an initial treatment with curative intent. The most successful of these regimens is M-VAC (methotrexate, vinblastine, adriamycin (doxorubicin), cisplatin) and significant clinical downstaging has been reported in 70% of 50 patients with T2-4 carcinomas. Thirty

of these patients went on to pathological staging by cystectomy and 10 were found to have a pathological complete remission (Scher *et al.*, 1988). The CMV programme (cisplatin, methotrexate, vinblastine) was used to treat 17 patients with locally invasive bladder cancer, 11 of whom achieved a complete response (Meyers *et al.*, 1985). We have previously reported the results of treatment with MVMJ and described an encouraging early response rate with limited toxicity (Waxman *et al.*, 1989). Because of the increasing interest in the use of chemotherapy for locally advanced disease, it is important to define response discriminants and the inter-relationship between newer investigative programmes and conventional therapy using radiation treatment. We present an analysis of patients with advanced bladder cancer who received MVMJ chemotherapy.

Patients and Methods

A total of 72 patients were referred for chemotherapy. Four did not receive chemotherapy, 3 were medically unfit and 1 refused treatment. Two patients received adjuvant treatment, 1 had prior chemotherapy and 1 received only 1 treatment cycle. These patients are excluded from this analysis. There were 7 deaths within the first month of treatment, 6 from urothelial cancer and 1 from a pulmonary embolus. These 7 patients are included in the analysis of response.

Thus 64 patients were evaluable for response; 49 were male and 15 were female. Their median age was 66 years (range 37–78). They received a median of 4 cycles of chemotherapy (range 1–6). Patients were staged by the TNM classification of the UICC (1978); 37 had locally advanced and 27 had metastatic urothelial cancer.

Chemotherapy consisted of methotrexate 50 mg/m² on days 1 and 15, vinblastine 3 mg/m² on day 1, mitozantrone 10 mg/m² on day 1 and carboplatin 200 mg/m² on day 1 of a 28-day treatment cycle. Folinic acid 15 mg was given as a single oral dosage on days 2 and 16. The toxicity of treatment and adjustments to dosage have been previously described (Waxman *et al.*, 1989).

Radical radiotherapy was generally given at a dosage of 40 Gy in 20 fractions to the whole pelvis and 20 Gy in 10 fractions to the true pelvis. Treatment was given over 6 weeks. Palliative radiotherapy usually consisted of a single fraction of 8 Gy to the true pelvis.

Responses were classified as follows. A pathological complete response was recorded when biopsy of the original lesion, but not cystectomy, had been

performed to confirm histological evidence of remission. Clinical complete remission indicated radiological evidence of complete tumour regression. A partial response was defined as reduction in metastatic tumour by more than 50% or downstaging of invasive to superficial disease in the bladder. Stable disease or no response comprised an improvement of less than 50% but less than 25% progression.

Results

The overall response to chemotherapy of the 64 treated patients was as follows: 10 (16%) achieved a pathologically documented complete remission, 7 (11%) a clinical complete remission, 12 (19%) a partial response, 15 (23%) stable disease and 13 (20%) progressive disease. Eighteen patients with locally advanced tumours responded to treatment. The median duration of response was 441 days (range 101–1131+). The median duration of response of 10 of these patients achieving a pathologically documented complete response was 490 days (range 204–1131+) and their median survival has not been reached. Eleven patients with metastatic tumour responded to chemotherapy. Their median duration of response was 241 days (range 72–517) and median survival 497 days (range 184–673+). The responses to chemotherapy of patients with locally advanced disease and those with metastatic disease are described in more detail in Tables 1 and 2.

The difference in survival between responding and non-responding patients was statistically significant ($P < 0.001$ (Log Rank analysis)). Table 3

Table 1 Response to Chemotherapy in Patients with Locally Advanced (NO MO) Urothelial Cancer

Response	No. of patients	Median response (range) (days)	Median survival (range) (days)
PCR	10	490 (204–1131+)	Not reached (550–1131+)
CR	2	232 (232–395)	356 (356–790+)
PR	6	290 (107–685+)	519 (256–1184+)
SD	11	—	350 (167–858+)
PD	7	—	180 (43–551)
ED	1	—	—
Total	18 36 (+1)	441 (107–1131+)	385 (43–1184+)

PCR = Pathological complete response.

CR = Complete response

PR = Partial response.

SD = Stable disease.

PD = Progressive disease.

ED = Early deaths.

Table 2 Response to Chemotherapy in Patients with Metastatic Urothelial Cancer

Response	No. of patients	Median response (range) (days)	Median survival (range) (days)
CR	5	235 (98–497)	497 (184–673+)
PR	6	242 (72–517)	247 (111–530)
SD	4	—	365 (271–1260+)
PD	6	—	175 (135–269)
ED	6	—	—
Total	11	241 (72–517)	—
	21 (+6)		271 (111–1260+)

CR = Complete response
 PR = Partial response
 SD = Stable disease.
 PD = Progressive disease.
 ED = Early deaths.

Table 3 Response to Chemotherapy According to Tumour Histology

Response	Squamous	G3	G2	G1	GX	CIS	AC	SM
CR	2	11	1			1	1	1
PR	2	6	2	1	1			
SD		10	2	2				1
PD	1	6	4		2			
NE	1	3	1		1		1	

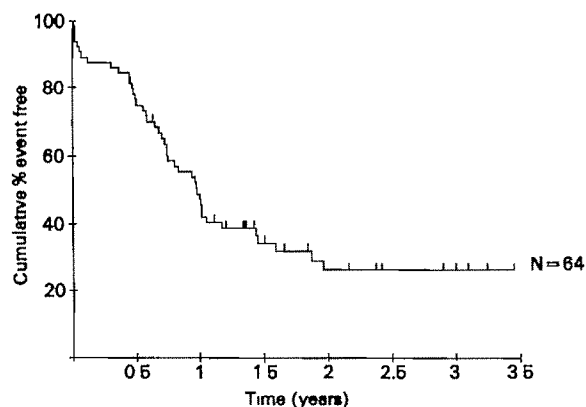
(Early deaths excluded)

CR = Complete response.
 PR = Partial response
 SD = Stable disease
 PD = Progressive disease
 NE = Not evaluable.
 Transitional cell carcinoma
 G1 = Well differentiated.
 G2 = Moderately differentiated.
 G3 = Undifferentiated.
 GX = Unknown,
 CIS = Extensive *in situ*.
 AC = Adenocarcinoma.
 SM = Squamous metaplasia.

shows the response to chemotherapy according to tumour histology and the Figure shows the actuarial survival of all evaluable patients.

Seventeen patients had radiotherapy prior to chemotherapy; in 15 patients this was to the bladder, in 1 to supraclavicular nodal secondaries and in 1 to cerebral metastases. Thirteen of the 15 patients treated with pelvic radiotherapy received radical radiotherapy with curative intent; 22 patients had pelvic radiotherapy after failure of chemotherapy, 11 of whom received radical radiotherapy. The responses to chemotherapy and radiotherapy are given in Table 4 and the disease-free interval and overall survival in Table 5.

In those patients who received chemotherapy after radiotherapy there were 6 responders to chemotherapy and 9 responders to radiotherapy.

**Fig.** Actuarial survival of all patients

There was no significant difference in the interval between radiotherapy and chemotherapy in chemotherapy responders when compared with non-responders (median 458 days, range 242–848 in responders; median 504, range 38–802 days in non-responders). Response was unrelated to tumour histology.

Nine of the 22 patients who received radiotherapy after chemotherapy had previously responded to chemotherapy. Eleven patients in this group had radical radiotherapy and 2 responded. Of these two patients, 1 patient died from iatrogenic hyperkalaemia at the completion of radiotherapy. This patient received radiotherapy to consolidate a partial response to chemotherapy. The second patient had persistent invasive disease after chemotherapy, downstaged to superficial disease after radiation; he died of urothelial cancer 10 months after completing treatment. None of the 11 patients treated with palliative radiotherapy responded. Two patients within the group who had not responded to chemotherapy or radiotherapy proceeded to cystectomy after failure of radiotherapy. One patient survived 18 months and the other is alive 29 months from the first day of chemotherapy.

Discussion

MVMJ chemotherapy is an effective form of treatment for bladder cancer and in 64 patients evaluable for response there were 17 (27%) complete clinical or pathological remissions and 12 (19%) partial remissions with 15 (23%) stable disease. The median duration of remission and survival was

Table 4 Response According to Treatment Modality

Treatment	No. of patients	Response to chemotherapy			Response to radiotherapy		
		CR + PR (%)	SD (%)	PD (%)	PR + CR (%)	SD (%)	PD (%)
MVMJ	18	13 (72)	3 (17)	2 (11)	—	—	—
INITIAL MVMJ + PRT	11	5 (46)	3 (27)	3 (27)	0	4 (36)	7 (64)
INITIAL MVMJ + RRT	11	4 (36.5)	4 (36.5)	3 (27)	2 (18)	2 (18)	7 (64)
INITIAL PRT + MVMJ	2	1	1	1	1	2	1
INITIAL RRT + MVMJ	13	5 (38)	4 (31)	4 (31)	8 (61)	4 (31)	1 (8)

PRT = Palliative radiotherapy

RRT = Radical radiotherapy

Radiotherapy groups exclude 2 patients not treated with pelvic RT.

CR = Complete response

PR = Partial response.

SD = Stable disease

PD = Progressive disease

similar for patients with locally advanced and metastatic urothelial cancer. In those patients who achieved a complete or partial response to chemotherapy or had stable disease, the survival extends up to 42 months. Prolonged responses in the stable disease group may reflect the methods of assessing stable disease and partial response. In bladder cancer, a similar situation may arise as with teratoma and lymphoma, in which radiological assessment may not differentiate between post-treatment fibrosis and active disease. In our study, pathological documentation of response required biopsy of the original disease site. This differs from the Memorial Sloan Kettering Hospital response criteria, which require complete surgical removal (Scher *et al.*, 1988).

In the present study there was only a small group of patients with tumours of atypical histology and their response rate was comparable to that of patients with transitional cell cancer. Similarly, the G3 tumours seemed to respond in a comparable fashion to the G1 and G2 cancers.

In this study, the relationship between radiother-

apy and chemotherapy was examined. Although patients were not treated in the context of a randomised trial of radiotherapy versus chemotherapy and numbers are small, information concerning the inter-relationship of responses to these treatment modalities has previously not been available. Five (23%) complete responses to chemotherapy following prior radiotherapy were seen, 2 of which occurred in patients unresponsive to radiotherapy. Thus a failure to respond to radiotherapy did not appear to predicate a failure to respond to chemotherapy. Considering this group as a whole, the response to chemotherapy was similar to that described in patients who had not had previous radiation therapy. The situation appeared different for those patients who received radiotherapy after chemotherapy. In this group there was only 1 complete response. In this patient there had been a response to chemotherapy. Thus failure to respond, or relapse after an initial response to chemotherapy, indicates a poor prognosis for subsequent radiotherapy. However, in the 2 patients treated by cystectomy, survival was 18 and 29+ months.

Table 5 Disease-free Interval and Overall Survival from Date of First Treatment

Treatment	No. of patients	Disease-free interval Median (range)	Overall survival Median (range)
MVMJ alone	18	Not reached (71–1260+)	Not reached (111–1260+)
INITIAL MVMJ + PRT	11	241 (173–517)	274 (175–530)
INITIAL MVMJ + RRT	11	264 (107–868)	352 (163–868+)
INITIAL PRT + MVMJ	2	207 (207–477)	261 (261–838)
INITIAL RRT + MVMJ	13	853 (329–1628)	1073 (329–1628+)

PRT = Palliative radiotherapy.

RRT = Radical radiotherapy.

RT groups exclude patients who did not have pelvic radiotherapy

The disease-free survival and overall survival were of a similar order in patients treated with chemotherapy alone or with chemotherapy followed by radiotherapy, including those treated with radical radiotherapy after chemotherapy. However, patients who received radiotherapy as their initial treatment, particularly those treated with radical radiotherapy in the first instance, had a significantly longer disease-free survival and overall survival than patients who received chemotherapy as their initial or only treatment. The median survival for patients having radical radiotherapy first was more than 4 times as long as the median survival of patients receiving radical or non-radical radiotherapy after chemotherapy or chemotherapy alone. This is likely to have been due to selection bias, with good prognosis patients, such as those with a long disease-free interval, likely to have been referred for chemotherapy for relapsed bladder cancer following radiotherapy.

These observations, although made in small groups of selected patients, have implications for the future planning of treatment and research in patients with advanced urothelial cancer. Both radiotherapy and chemotherapy are associated with significant morbidity, and treatment involves a considerable time period relative to the patient's life expectancy.

In the context of this analysis of chemotherapy given as primary treatment for bladder cancer, subsequent radiotherapy after failure of chemotherapy is unlikely to be curative. Where chemotherapy follows radiotherapy, response is seen and not precluded by prior disease progression.

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Analysis of Continent Versus Standard Urinary Diversion

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Summary—The seemingly high complication and re-operation rates associated with continent urinary diversion have led some to criticise its morbidity and question its role in reconstructive urological surgery. We therefore reviewed our experience with all patients undergoing either continent or standard urinary diversion performed by 3 urological surgeons during a specified 3-year period. In 73 consecutive patients (22 continent urinary diversion, 51 standard urinary diversion), no significant difference was demonstrated with respect to the number of post-operative in-hospital days, complication rate, re-operation rate and operative mortality rate between the 2 groups. While those undergoing continent diversion were on average younger and healthier than their counterparts receiving standard diversion, stratification of patients in each group according to age and a pre-operative "fitness" score showed no significant difference in operative mortality or major morbidity between comparable patients in each group. The mean post-operative length of hospital stay was, however, 3 days shorter for the youngest and fittest patients receiving standard versus continent urinary diversion.

The first non-faecal continent diversion was described by Couvelaire 35 years ago (Couvelaire, 1951). Urological surgeons have since explored innovative and effective ways of fashioning various bowel segments into continent urinary reservoirs. Gilchrist, working concurrently with Bricker, described the use of a caecoileal segment for continent urinary diversion (Gilchrist *et al.*, 1950). Camey used Couvelaire's concept of an intestinal reservoir anastomosed directly to the urethral stump and reported results with his procedure in 87 patients in 1979 (Camey and LeDuc, 1979).

Kock advanced the field of urological reconstructive surgery when he described the continent non-refluxing ileal reservoir which he had first developed for ileostomy patients after total proctocolectomy (Kock *et al.*, 1985a, b). Several authors, in particular Skinner, have reported their considerable experience with modifications of the "Kock pouch"

(Skinner *et al.*, 1987). While early complication and re-operation rates were unacceptably high, many of the difficulties with the technique have since been resolved with a subsequent decrease in these rates. Numerous other operative procedures have been suggested as the ideal urinary reservoir for the patient facing bladder removal (Mansson *et al.*, 1985; Rowland *et al.*, 1985; McDougal, 1986; Lockhart, 1987; Reddy *et al.*, 1987; Sarosdy *et al.*, 1987; Hautmann *et al.*, 1988; Melchior *et al.*, 1988). The availability of so many surgical options attests to the lack of unanimity among urologists as to the selection of a single technique that satisfies completely the quest for a low pressure, non-refluxing, continent and cosmetic reservoir with an acceptable complication and re-operation rate.

While the most recent trend is toward increasing acceptance of continent urinary diversion, there have been questions raised regarding the advisability of performing continent urinary diversion secondary to its presumed high cost in terms of hospital stay, operative complications and risk of

re-operation (McDougal, 1987). To address these concerns, we report our institutional experience comparing continent urinary diversion with the standard ileal conduit. These procedures were carried out by the same surgeons at the same institution. We included all patients who had either procedure performed in a 3-year period extending from 1986 to 1989 and analysed their care with respect to length of hospital stay, surgical mortality, early and late complications, and need for re-operation.

Patients and Methods

From March 1986 to August 1989, 73 adult patients underwent either continent urinary diversion or ileal conduit urinary diversion performed by 3 surgeons at this institution. The majority of patients received a modification of the caecoileal pouch described previously (Rowland *et al.*, 1985). Standard urinary diversion was performed according to the technique described by Bricker (1950) and Butcher *et al.*, (1962). Patients were offered a choice of either type of diversion after a full explanation of the advantages and disadvantages, as well as complications, of both procedures. In general, continent diversion was not offered to the elderly, the morbidly obese, or those with significant intercurrent medical illnesses.

In total, 51 patients underwent standard ileal conduit diversion. Of these, 43 underwent concomitant radical cystoprostatectomy with pelvic lymph node dissection for invasive bladder carcinoma (41 patients) or recurrent localised prostate cancer (2 patients) following primary radiotherapy. The remainder received a urinary diversion alone for complications of prior pelvic radiotherapy, for chronic interstitial cystitis, or for unmanageable colo-vesical fistula due to colon or prostate cancer. The patients ranged in age from 43 to 85 years, (mean 67). The mean follow-up was 15.5 months, ranging from 6 to 42 months.

The remaining 22 patients underwent some form of continent urinary diversion. Of these, 19 received a modification of the right colon pouch (Rowland *et al.*, 1985), 2 patients received a hemi-Kock neobladder (Skinner *et al.*, Marketing communications, 3M Medical-Surgical Division), and 1 patient received a detubularised sigmoid neobladder. Nineteen of the 22 patients underwent concomitant radical cystectomy for invasive bladder carcinoma. One patient underwent concomitant radical cystoprostatectomy for prostate cancer locally invasive of the bladder neck. The remaining 2 continent

diversions were performed in bladder exstrophy patients who had prior urinary diversion: 1 with an ileal conduit and 1 with cutaneous ureterostomies. The patients in this group ranged in age from 22 to 73 years (average 58). The mean follow up was 13.6 months (range 1–25).

Length of post-operative hospital stay was obtained from the hospital records. Operative mortality was defined as any case in which the patient died within 30 days of the operation or in which the cause of death was clearly a consequence of the operation. Early post-operative complications included any adverse medical or surgical condition occurring within 30 days of operation or during the initial hospitalisation (if longer). Late complications, other than simple urinary tract infection, included any adverse medical or surgical condition treated after this initial period. These were identified from the patient's case notes. All complications which occurred on or before 1 September 1989 were included.

In order to assess each group's average pre-operative "fitness" and its effect on post-operative morbidity and mortality, we scored each patient according to a pre-operative assessment of fitness score (PAFS) (Playforth *et al.*, 1987). This score assesses 26 items including age, chronic disease and acute presenting illness, with the total fitness for any patient ranging from 0 (fit) to 10 (unlikely to survive). In 1517 consecutive patients studied, an increase in PAFS correlated significantly with an increased rate of operative mortality and of major complications. All patients in both groups had ureteroileal or ureterocolonic anastomoses stented by ureteric catheters. Stent studies were performed prior to stent removal. In addition to stent studies, radiological pouch studies were obtained in all patients undergoing continent urinary diversion. Most patients in both groups had a post-operative IVU carried out at 1 to 3 months following surgery.

Either the Student's 2-tailed *t* test, corrected when appropriate for unequal variances, or the chi-square test, depending on the appropriate circumstance, was used to assess statistical significance between groups for mean age, mean number of post-operative hospital days, operative mortality rate, early and late complication rate, and re-operation rate.

Results

Analysis of age at surgery showed the continent urinary diversion group to be significantly younger than the ileal conduit group. The PAFS was also

significantly lower in the continent diversion group. The groups were not significantly different with regard to concomitant cystectomy rate (Table 1). The results of the comparative analysis of both groups with regard to post-operative hospital stay, operative mortality, early and late complication rate and re-operation rate are shown in Tables 2 to 4.

The mean number of post-operative hospital days was not significantly different for the 2 groups.

Table 1 Details of Patients

	Continent diversion	Ileal conduit	P
No of patients	22	51	
Average age (years)	58	67	0.003
Average fitness score	0.7	3.6	<0.0005
Diversion with cystectomy	20 (91%)	47 (92%)	0.86

Table 2 Early and Late Complications: Ileal Conduit (n = 51)

<i>Early</i>		
Wound infection		6
Wound dehiscence		1
Urosepsis		2
Prolonged ileus		2
Deep vein thrombosis		
Lower extremity		2
Upper extremity		2
Simple IV phlebitis		1
Pulmonary embolus		4
Ureteric leak		2
Enterocutaneous fistula		1
Confusion		2
Supraventricular tachycardia		1
Ventricular tachycardia		1
CVA		1
Parotiditis		1
<i>C. difficile</i> enterocolitis		3
Total		32
Total patients		25
<i>Late</i>		
Urosepsis		1
Small bowel obstruction		1
Small bowel perforation		1
Pelvic abscess		1
Ant. abd. wall abscess		1
Hernia		
Incisional		1
Parastomal		
Ureteric stricture		2
Stomal stenosis		1
Total		9
Total patients		8

Table 3 Early and Late Complications: Continent Diversion (n = 22)

<i>Early</i>	
Wound infection	3
Urosepsis	1
Parastomal abscess	1
Pyelonephritis	2
Deep vein thrombosis	
Lower extremity	
Upper extremity	1
<i>C. difficile</i> enterocolitis	1
Bilat. ant. fem. cut. neuropathy	1
Supraventricular tachycardia	1
Total	11
Total patients	11
<i>Late</i>	
Pyelonephritis	1
Stomal stenosis	1
Uretero-enteric obstruction	2
Hernia	
Incisional	1
Parastomal	1
Incontinence	1
Total	7
Total patients	5

Table 4 Comparison of Continent and Standard Urinary Diversion

	Continent	Standard	P
Mean post-op. hospital days	17.7	18.3	0.77
Median post-op. hospital days	16	15	
Complication rate (% pts.)			
Early	50%	49%	0.94
Late	23%	16%	0.47
Major* (early and late)	36%	24%	0.26
Re-operation rate (% pts.)	13.6%	9.8%	0.63
Op. mortality rate (% pts.)	0.0%	2.0%	0.51
Total op. mortality	1.4%		

* Major complications exclude simple wound infection, prolonged ileus, *C. difficile* colitis, incisional hernia, DVT, simple IV phlebitis, post-operative confusion, supraventricular tachycardia, parotiditis and transient neuropathy.

The mean number of post-operative days for the continent diversion group and the ileal conduit group were 17.7. and 18.3 days respectively. The median number of post-operative days for the continent diversion group and the ileal conduit group were 16 and 15 days respectively ($P=0.77$).

There was one peri-operative death in the standard diversion group and no peri-operative deaths in the continent diversion group. Differences in complication rates and re-operation rates did not achieve statistical significance between the 2 groups (Table 4).

When stratifying each group according to age or pre-operative fitness, no statistically significant difference in mortality, major complication or re-operation rates could be detected between comparable patients. However, in the 48 healthiest patients, those with a PAFS less than or equal to 2, the mean number of post-operative hospital days was 3 days shorter for the standard urinary diversion group than the continent diversion group ($P=0.02$).

Non-operative complications

Most of the complications experienced in both groups were relatively minor, requiring conservative (non-operative) therapy (Tables 2 and 3). For example, one-third of the early complications in the ileal conduit group comprised either deep venous thrombosis, infection of urine or wound, or *C. difficile* colitis. Similarly, in the continent diversion group, more than two-thirds of the early complications fell into these same categories. There were 8 early complications owing to thromboembolic phenomena in the ileal conduit group, while only 1 in the continent urinary diversion group. Only 1 patient has an unacceptable degree of wetting. One patient had difficulty in catheterising her pouch; this was solved by instructing her in clean intermittent catheterisation with the use of a Coudé tip catheter. All other patients report no difficulty in catheterisation. The 3 patients who received bladder replacement are continent during the day and wear condom catheters at night.

Re-operative surgery

Five patients in the ileal conduit group required secondary surgical procedures. Of these, 2 required small bowel resection or bypass. These patients had been previously irradiated. One patient required early re-operation for wound dehiscence and has done well since. One patient required a stomal revision for stomal stenosis and continues to have problems with uretero-enteric stenosis currently being managed by periodic balloon dilatation. Finally, 1 patient required incision and drainage of an anterior abdominal wall abscess.

Three patients in the continent diversion group underwent additional surgical procedures. One patient underwent an elective incisional herniorrhaphy to repair a hernia which developed after an early post-operative wound infection. One patient was explored for a recurrent parastomal abscess but no fistulous tract to the efferent limb of her urine reservoir was detected. The third patient developed ureteric obstruction secondary to a parastomal hernia which required re-operation 6 months post-operatively. The patient subsequently developed a stomal stenosis, requiring another operation 11 months after his initial radical cystectomy.

Discussion

The literature is replete with various series reporting experience with the Bricker ileal conduit diversion, and reports of the modern experience with continent urinary diversion have appeared within the last 3 years. A total of 958 cases of cystectomy with ileal conduit diversion and 1062 cases of cystectomy with continent urinary diversions of various types are presented with their respective operative mortality rates, complication rates and re-operation rates for comparison (Tables 5 and 6).

Table 5 One-stage Radical Cystectomy with Ileal Conduit Diversion

Author	Dates	No of patients	Operative mortality (%)	Re-operation rate (%)		Complication rate (%)	
				Early	Late	Early	Late
Pernet and Jonas (1985)	1958-81	132	8	15	17	46	32
Daughtry <i>et al</i> (1977)	1960-70	55	9	—	—	22	4
Sullivan <i>et al</i> (1980)	1956-71	336	14	—	—	43	52
Johnson and Lamy (1977)	1969-75	214	3.3	—	—	28	41
Svare <i>et al</i> . (1985)	1973-80	110	4.6	23	22	28	57
Neal (1985)		111	0	—	23	—	63
Total		958					

Table 6 Modern Experience With the Continent Diversion

Author and type	Dates	No of patients	Operative mortality (%)	Re-operation rate (%)			Complication rate (%)		
				Early	Late	Total	Early	Late	Total
Kock <i>et al.</i> (1985) "Kock"	1975-84	31	0	6.4	81	87.4	6.4	81	87
deKernion <i>et al.</i> (1985) "Kock"	1983-84	22	4.5	—	—	32	—	—	—
Waters <i>et al.</i> (1987) "Kock"	1984-86	15	0	20	13	33	20	20	40
Skinner <i>et al.</i> (1987)	1982-85	250	2	—	—	31	16	31	47
Skinner <i>et al.</i> (1989) "Kock"	1982-88	531	1.9	—	—	18*	16	32	48
Camey (1985) "Camey"	1958-85	150	3.3	—	—	—	—	—	43
Allen <i>et al.</i> (1985) "Camey"	1984-85	11	0	0	0	0	18	9	27
Thuroff <i>et al.</i> (1988) "Mainz"	1983-87	100	0	3	14	17	7	18	25
Mansson <i>et al.</i> (1985) Caecal reservoir	1977-85	27	3.7	15	59	74	19	70	89
Rowland <i>et al.</i> (1987) "Indiana"	1982-86	29	0	4	24	28	—	—	—
Montie <i>et al.</i> (1987) Varied diversions	1984-86	33	0	—	—	21	—	—	—
Wenderoth <i>et al.</i> (1990)	1986-89	113	0	4	8	12	43	17	60
Total		1062							

* Re-operations for incontinence only

A comparison of these reports reveals that the reported operative mortality rate was lower for the continent diversion group, 7.8% versus 1.6%, than for the standard ileal conduit group. Crude rates for re-operative surgery were comparable in both groups, approximately 33%.

These crude comparisons suffer from several shortcomings and are made only to lend historical perspective. Comparing conduit series from the 1950s and 1960s with more recent series of continent diversions disregards the effect of advances in modern surgical management such as pre- and post-operative intensive care, and surgical nutrition which alone may influence both operative mortality and morbidity. This is probably reflected in the lower operative mortality rate for the continent diversion series, which are predominantly from the 1980s.

In addition, the large published series of ileal conduit urinary diversions often report 10 or 20 year follow-up, while the continent diversion series are for the most part newer with much shorter follow-up. Comparison of crude complication and re-operative surgery rates will always favour the newer treatment with, invariably, the shorter follow-up.

Finally, a review of the types of re-operations

carried out in both groups reveals fundamental differences. While patients in the conduit series had a predominance of major complications requiring re-operation for problems like ureteric leaks, stomal stenoses or renal stones, the majority of re-operations in the continent diversion group were solely for problems with the continence mechanism.

High complication and re-operation rates for continent diversion are the rule rather than the exception, owing to the gradual learning curve associated with these more challenging procedures. This high re-operation and complication rate has been a formidable barrier to the widespread acceptance of the continent urinary diversion and has led some to criticise both the cost and the concept of such procedures (McDougal, 1987).

We conducted the present review in order to evaluate the true cost of continent urinary diversion in a highly select cohort of patients undergoing either standard or continent urinary diversion by a limited number of surgeons in a single institution, mindful of the limitations of retrospective comparative analyses. Limiting our review to these patients provided an opportunity to assess the cost of continent versus standard urinary diversion as judged by differences in hospital stay, operative mortality, early and late complications, and the

need for re-operative surgery in a simultaneous series of patients. The review suggests that, judged by these criteria, continent urinary diversion can be provided to patients facing bladder removal at a cost no greater than that experienced with the standard ileal conduit. Stratification of patients into groups with a similar PAFS shows a small decrease in the mean length of hospital stay for those undergoing standard urinary diversion, but no difference in operative mortality, complication rate or re-operation rate.

One of the reasons why the present series shows an acceptably low complication and re-operation rate may be the relative simplicity of the operation used in the majority of patients in the continent urinary diversion group. Specifically, uretero-colonic anastomoses have been part of the standard urological repertoire for years (Leadbetter, 1952). The efferent continence mechanism is supplied by a tapering and imbrication of the ileal segment without the need for the creation of an intricate nipple valve with its inherent problems.

Our experience with a consecutive series of patients undergoing urinary diversion suggests that continent diversion can be performed for patients facing bladder removal with an acceptable risk that is similar to that experienced with the standard ileal conduit. Complications have been managed for the most part non-operatively, continence is excellent, and in general no early upper tract abnormalities have been noted. While physician bias in selecting younger, healthier patients for continent diversion might have prejudiced our findings in favour of this group, upon further analysis this did not appear to be an important factor in achieving these comparable costs. It remains to be seen whether longer follow-up of this cohort of patients, as well as those who have undergone the myriad of other continent urinary diversions available, will demonstrate significant improvement in upper tract survival and decrease in late complications and re-operations compared with their counterparts who have received ileal conduits.

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A Prostatectomy Audit: Phase I—Insights and Questions

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Summary—A local prostatectomy audit is being undertaken to gain some insight into the pre- and peri-operative factors that influence post-operative outcome and length of post-operative stay. The aims of the first phase of the audit, involving 150 prostatectomy patients, have been to attempt to define the minimum data set required to meet the study's objectives, and to devise a data-collecting tool that can be completed by the medical and nursing staff as part of the routine work. A tentative model has been devised to forecast post-operative stay. The audit has raised a number of questions which will form the basis of further studies.

Every organisation has a responsibility to monitor the quality of its activities, to identify areas where quality is below an agreed standard and to take appropriate remedial action. Pressures on clinicians to introduce methods of clinical audit, aimed at quality assurance, are coming from the Government, Royal Colleges, hospital management and from within the profession itself. The Government White Paper "Working for Patients" recognises that the most effective studies are likely to be internally generated with local peer group review of the data under analysis.

Many claims have been made for the benefits of clinical audit, including reduction in peri-operative mortality and post-operative complications (Grier *et al.*, 1986), increased organisational efficiency and enhanced skills in self-evaluation (Coles, 1989). Priorities for audit include high volume procedures, high risk procedures and procedures where there is some controversy as to "best practice" (Shaw and Costain, 1989). Prostatectomy forms a large part of the urological workload in a District General Hospital. Unless the prostate gland is particularly large, transurethral prostatectomy has come to replace open prostatectomy, in the West, as the surgical treatment of choice for benign prostatic

hyperplasia. Recent studies suggest, however, that transurethral prostatectomy is less effective in overcoming urinary obstruction than is the open operation (Roos *et al.*, 1989) and patients undergoing transurethral prostatectomy have higher rates of re-operation (Roos and Ramsey, 1987; Wennberg *et al.*, 1987), a higher incidence of post-operative urethral stricture (Wennberg *et al.*, 1988) and a higher long-term mortality, even when identified as being at low risk (Roos *et al.*, 1989). For all of these reasons prostatectomy was selected for clinical audit.

The aims of the audit are to determine the influence of pre- and peri-operative factors on post-operative outcome, to identify patients who have a high risk of developing post-operative complications and to forecast the length of their stay, and to identify ways of improving organisational efficiency.

The success of any audit in meeting its objectives depends on the accuracy and completeness of the data under review (Pollock, 1990). This in turn is affected by the level of commitment of all participants (Ellis, 1989), the availability of resources (both human and technological) (Gough *et al.*, 1980; Shaw, 1990) for data collection, analysis of results, and the development of a data-collecting method which is quick, reliable (Whates *et al.*, 1982; Skinner *et al.*, 1988) and easily incorporated

into routine work (Gough *et al.*, 1980; Grier *et al.*, 1986). The aim of the first phase of the audit was therefore to decide on the minimum amount of data to be collected which would be consistent with the objectives of the study and to devise a data-collecting proforma which could be completed by medical and nursing staff as part of the routine work.

Patients and Methods

An in-depth prospective pilot study of 150 prostatectomy patients was carried out from July 1989 to February 1990 in a District General Hospital with 3 part-time consultant urologists. A research nurse was employed for 3 days a week to collect and collate the data for the first phase of the audit and to co-ordinate the activities of the group, arrange meetings and review data-collecting methods. She recorded information on the patients' past medical history, pre-operative assessment and post-operative events while in hospital, and visited the patients in their home 2 weeks after discharge to assess the impact of any urological problems, the patients' satisfaction with their progress and with the information that they had received while in hospital. The nursing staff on the urology ward kept a diary of the patients' post-operative problems, for comparison with the entries in the medical notes, and on a separate proforma the surgeons recorded events in theatre, including the duration of operation, the weight of prostatic tissue removed and any problems encountered.

Monthly meetings were held to review the data and to decide whether or not the post-operative complications which had arisen were avoidable, and if possible to identify any contributory factors. It was established at the outset that the content of the discussions would be confidential to the group. After data had been collected on 100 patients the initial data-collecting forms were streamlined and a computerised system developed to aid analysis. This involved creating patient record forms using an EPI INFO software package given to the group free of charge by the community statistician. Detailed analysis of the first 150 patients was then undertaken further to streamline the data-collecting methods, and a tentative model developed to aid prediction of post-operative stay.

Results

Of the 150 patients in the first phase of the audit, 8 (5.3%) underwent retropubic prostatectomy and

the remainder transurethral prostatectomy. The mean age of the patients was 70.4 and 69.1 years respectively. There was no significant difference in the patients dealt with by the 3 urologists, by age or by admission type. Emergency or very urgent admissions (within 1 week of referral) constituted 38%. Of these, 35.1% were admitted via casualty, 14% were transfers from day-bed investigations and 26.3% came from other wards within the hospital (orthopaedic, general surgical and medical), usually with retention of urine. Of the arranged admissions 52.5% underwent operation within 5 weeks and 72.8% within 10 weeks of inclusion on the waiting list.

Table 1 summarises the nature and incidence of immediate post-operative complications thought to be related, at least in part, to the transurethral prostatectomy. Six patients failed to re-establish a normal pattern of micturition during their post-operative hospital stay. Of these, 5 were discharged with a urethral catheter and 1 with a suprapubic catheter. Two patients required a repeat transurethral prostatectomy on the same admission. Three patients died of unrelated medical conditions.

Complications after retropubic prostatectomy included wound infection and haematoma.

The case for the prophylactic use of antibiotics in transurethral surgery is not clear cut (Christensen and Madsen, 1990). At Stirling, 2 of the 3 consultants routinely prescribed 250 m ciprofloxacin with the premedication and 1 h before catheter removal, while 1 did not. Five patients received only 1 dose of ciprofloxacin in error. Prophylactic administration of 2 doses of ciprofloxacin would appear to reduce significantly the incidence of post-operative urinary tract infection (Table 2). It must be pointed out, however, that this was *not* a randomised trial but merely a depiction of the outcome of existing but differing practice. One interesting observation was the emergence of a

Table 1 Post-operative Complications following Transurethral Prostatectomy in 142 Patients

Complication	No. of patients	Rate
Urinary tract infection	22	15.5
Retention after catheter removal	17	12.0
Minor haemorrhage	13	9.2
Septicaemia	2	1.4
Water intoxication	1	0.7
Epididymitis	1	0.7
Myocardial infarction	1	0.7
Deep vein thrombosis	1	0.7

Table 2 Results of Audit of Prophylactic Antibiotic Policy in Patients undergoing Transurethral Prostatectomy

<i>Ciprofloxacin</i>	<i>Post-operative urinary tract infection</i>			<i>Total</i>
	<i>No</i>	<i>Yes</i>	<i>Coagulase negative staphylococci</i>	
Not given	19	9	1	29
With premedication only	5	0	0	5
With premedication and before catheter removal	45	1	7	53
Total	69	10	8	87

Patients excluded from analysis: Concurrent antibiotics for pre-operative urinary tract infection 27, Antibiotics for other infections 15; No results 13; Total exclusions 55.

multiple antibiotic-resistant strain of coagulase-negative *Staphylococcus* in the group of patients receiving 2 doses of ciprofloxacin. This was quickly picked up by the audit and a collective decision taken not to treat the infection with nitrofurantoin (one of the few antibiotics to which it was sensitive) unless the patient was severely immunocompromised.

A tentative model forecasting the length of post-operative stay following transurethral prostatectomy has been devised and is now being tested "blind" by a registrar who has not been involved in the first phase of the data collecting and who is unaware of the weightings that have tentatively been assigned to each factor. For the first 150 patients the model predicted post-operative stay correctly in 78.2% of cases and plus or minus 1 day in a further 19% of cases. Admission factors which appear to delay discharge include active chest infection, pyrexia of unknown origin, age (Fig. 1, Table 3), general physical condition and anxiety.

Significant post-operative factors include retention of urine after catheter removal, septicaemia, water intoxication and pyrexia of unknown origin. Several factors unrelated to prostatectomy significantly increased post-operative stay for some patients, including social delays (awaiting collection by relatives or a place in a nursing home) and deterioration in physical condition unrelated to prostatectomy. Previous prostatectomy, minor post-operative haemorrhage and urinary tract infections did not affect the duration of stay.

The results of the community surveillance of patients 2 weeks after discharge, by the research nurse, showed that 95% of patients were satisfied with their progress or had only minor complaints and 96% were satisfied with the information received in hospital; 16% had visited their family

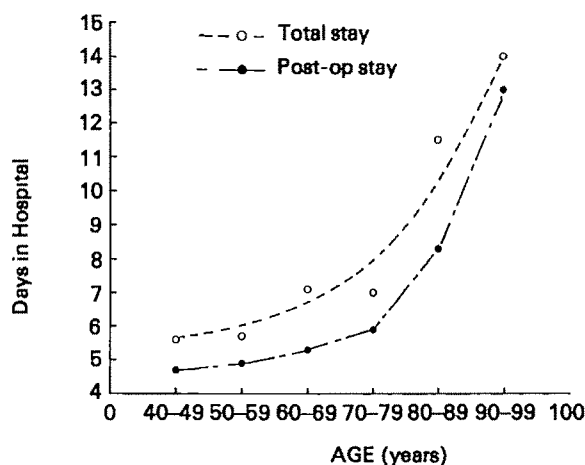


Fig. 1 Relationship between prostatectomy patients' age and duration of hospital stay. (See also Table 3 for additional data.)

doctor since discharge with a urological problem, mainly for possible urinary tract infections. Patients who had been operated on by the registrar were more likely to report that a urological problem was worse than before than were patients where the consultant had been the principal surgeon. Feedback received by the consultants at the routine outpatient clinic visit 4 to 8 weeks after discharge suggested that many patients had found the visit by the research nurse at the 2-week point to be reassuring.

Discussion

The success of any audit study in meeting its objectives depends on the accuracy and completeness of the data under review, which in turn is affected by many factors (Fig. 2).

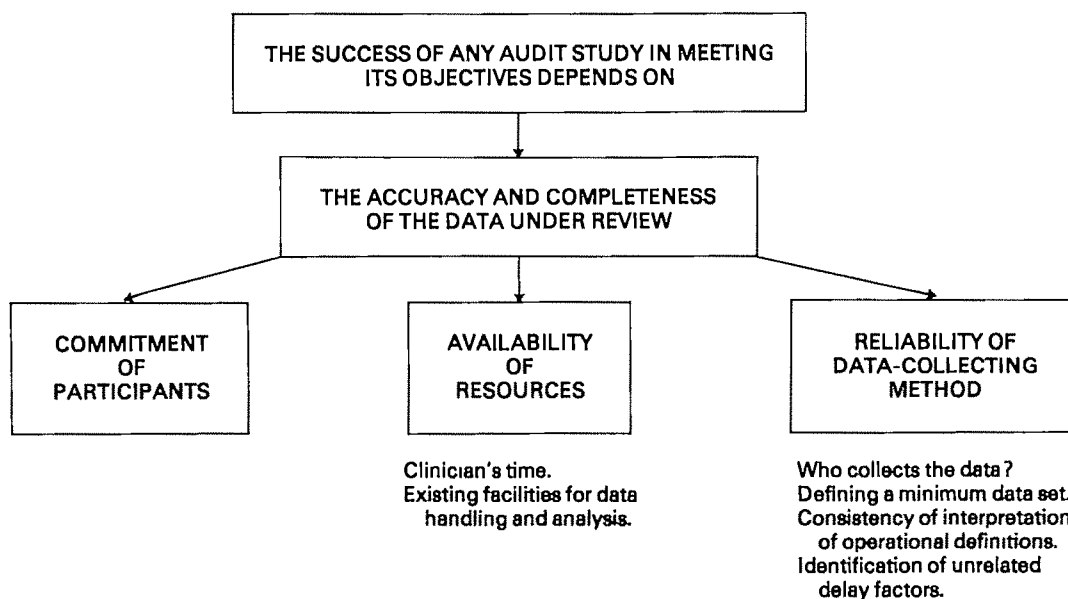
Table 3 Relationship between Age of Patient, Total Hospital Stay and Post-operative days following Prostatectomy

Age band (years)	Transurethral				Retropubic			
	No.	Total days	Post-op days	Pre-op days	No.	Total days	Post-op days	Pre-op days
40-49	7	5.6	4.7	0.9	0	—	—	—
50-59	16	5.7	4.9	0.8	0	—	—	—
60-69	45	7.1	5.3	1.8	4	9.3	8.3	1.0
70-79	51	7.0	5.9	1.1	3	9.7	8.0	1.7
80-89	22	11.5	8.3	3.2	1	46.0	35.0	11.0
90-99	1	14.0	13.0	1.0	0	—	—	—

It is easy to say that those with an interest in improving the standard of their work are likely to be those with little to fear from audit. In reality a certain caution before embarking on an audit project is both natural and rational. It is natural for a consultant to feel some unease about entering into a free and frank discussion of the avoidability of post-operative complications with peers, and even more so in front of junior staff. It is also natural to fear the uses to which data might be put by management, such as pressure on clinicians to reduce the number of high risk, expensive or long operations performed, simply in the name of surgical efficiency. Our own study confirmed that patients over 80 years of age had significantly

longer post-operative stays than younger patients, and for reasons often unrelated to the prostatectomy itself, such as awaiting a place for continuing care, or convalescence from a concurrent active medical problem present at the time of emergency admission or at the time of transfer from another ward. Although pre- and post-operative morbidity is high in this age group, the long-term outcome is generally good (Wyatt *et al.*, 1989), significantly improving the quality of life and justifying the decision to operate.

Resistance to audit manifests itself in many ways—rarely in outright aggression, more frequently as lip service to the concept of audit and no action. Any audit is doomed to failure if it does not

**Fig. 2** Factors affecting the success of an audit.

have the wholehearted commitment of all participants. To enable the group to feel confident when embarking on such a potentially hazardous project as an audit study it is therefore important that the leader of the group creates an atmosphere which encourages full and frank discussion (Campbell, 1988) and which does not turn into a witch hunt. At the beginning of this audit monthly meetings were held involving consultants, the registrar, the resident, ward sister and the research nurse. Now the meetings are held weekly. Considerable importance is placed on attending the meetings and there is no doubt that the audit has led to improved communication within the group and improved postgraduate teaching. A climate is being fostered which encourages enquiry, not only of the prostatectomy process and its outcome, but also of the firm's organisation, including the role of the registrar, ways of further reducing waiting list times and of reducing social delays to patient discharge. The feasibility of organising a routine visit to all patients 2 weeks after discharge by an experienced nurse is being actively considered.

Preliminary results are already pointing the way to further studies, such as an exploration of treatment alternatives for worst outcome groups and a further ciprofloxacin study to determine whether 1 or 2 doses administered orally is required for effective prophylaxis, and the optimum timing for this. While not resolving the debate about the need for prophylactic antibiotics in transurethral surgery, there would seem to be some merit in exploring the efficacy of oral as opposed to intravenously administered ciprofloxacin (Christensen *et al.*, 1989; Cox, 1989; Gambert *et al.*, 1989).

Validating the model which aims to predict the length of post-operative stay following transurethral prostatectomy is one of the major objectives of the second phase of the study and is now under way. If the model proves to be reliable and valid it will be a very powerful, objective tool for assessing outcome in the short term. A discrepancy of more than 1 or 2 days between a patient's actual and predicted stay indicates a possible problem which requires in-depth peer review. Unlike the days when monthly mortality and morbidity meetings were the only mechanism for peer review, it would not be possible for a mismanaged case to be effectively swept under the carpet, by self-deceit or by complacent and collusive self-justification within the group. Instead, answers would be sought to a number of questions. Should the operation have been performed at all? Could pre-and post-operative assessment and man-

agement have been better? Was the problem largely organisational—non-availability of a consultant at a critical point, misplaced laboratory results, *etc*? The tool could also facilitate more valid local and regional comparisons of post-operative morbidity and mortality data, protecting the competent surgeon from being castigated for "poor" results because he is prepared to operate on higher risk patients than is his neighbour.

A local initiative such as this study has many obvious limitations, not least of which is a limited sample size. Some post-operative complications such as septicaemia and septicaemic shock are relatively uncommon. Insights into the causes of less common complications, and wider issues, such as the role of the registrar, requires pooling of data by urologists, preferably throughout the UK. Before this can be achieved there needs to be a nationally agreed system for coding urological procedures and medical diagnoses, nationally agreed operational definitions of even the supposedly simplest parameters such as "urinary tract infection" and "minor haemorrhage" and a nationally agreed minimum data set to be collected by all participants as part of their routine work, with the possibility of additional parameters being added by clinicians to reflect local interests and local studies.

With a large pool of accurate prospective data the scope for subsequent studies would be enormous.

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Unusual Hyperechoic Appearance of Prostate Cancer on Transrectal Ultrasonography

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Summary—A series of 157 patients with prostate cancer underwent transrectal ultrasonography prior to radical prostatectomy. In 112 patients (71.3%) the tumours appeared hypoechoic relative to the echo pattern of the normal peripheral zone; in 43 (27.4%) they appeared isoechoic, and in only 2 (1.3%) did they appear purely or predominantly hyperechoic. These 2 hyperechoic tumours were unusual ductal adenocarcinomas with central necrosis and dystrophic calcification within solid tumour nests, a pattern similar to that of comedo-carcinoma of the breast. Calcification within prostate cancer was found in 4 of the 157 radical prostatectomy specimens, including 2 other hypoechoic cancers which contained intraluminal or psammomatous calcification. Although the most common sonographic appearance of localised prostate cancer is hypoechoic, a predominantly hyperechoic pattern is seen occasionally and suggests the presence of a high grade ductal adenocarcinoma.

Lesions within the prostate can be divided into 3 major groups on the basis of echogenicity: hypoechoic or echopenic lesions which are less echogenic than the normal peripheral zone; isoechoic lesions with sonographic characteristics similar to those of the normal peripheral zone tissue; and hyperechoic or echodense lesions which are more echogenic than the normal peripheral zone. A mixed echogenic pattern results when a lesion has both hypoechoic and hyperechoic areas (Rifkin *et al.*, 1989). Although a number of earlier studies reported that prostate cancer typically appeared hyperechoic (Resnick *et al.*, 1978; Rifkin *et al.*, 1983), Lee *et al.* (1985) presented the first convincing evidence that a hypoechoic area in the peripheral zone was a reliable criterion for the diagnosis of prostate cancer. Several subsequent studies have shown that prostate cancer does not always appear hypoechoic and that many lesions are, in fact, isoechoic (Dähnert *et al.*, 1986a,b; Griffiths *et al.*, 1987; Jones *et al.*, 1989; Shinohara *et al.*, 1989). The 2 unusual hyperchoic prostate cancers reported here com-

prised only 1 to 2% of the early stage prostate cancers we examined (Egawa *et al.*, 1989; Shinohara *et al.*, 1989). Both of these tumours demonstrated an unusual pathological pattern, a ductal adenocarcinoma with central necrosis and dystrophic calcification.

Case Reports

Case 1. A 64-year-old man received external beam radiotherapy (6800 cGy) beginning in June 1979 for a moderately differentiated (Gleason score 6) prostate cancer palpably confined to 1 lobe (clinical stage B1). In April 1987 he underwent a transurethral resection of the prostate (TURP) for lower tract obstructive symptoms. At that time he was found to have adenocarcinoma (moderately differentiated, Gleason score 7) in 75% of the chips. Rectal examination revealed a flat fibrotic prostate without nodularity. Metastatic evaluation included chest X-ray, computed tomography and magnetic resonance imaging of the abdomen and pelvis, radioisotopic bone scan, and evaluation of serum markers (acid phosphatase and alkaline phosphatase), which were within normal limits. Transrectal ultrasonography with the Aloka SSD 520 chair-type radial scanner equipped

with 7.0 MHz radial transrectal probe revealed a large hyperechoic area in the left peripheral and transition zones with acoustic shadowing (Fig. 1). In addition, there was a hypoechoic lesion in the right peripheral zone posteriorly, near the base, which bulged into the surrounding tissue. The hypoechoic lesion was interpreted as prostate cancer with extracapsular extension (Fig. 1A, arrowhead). The patient underwent salvage radical retropubic prostatectomy with bilateral pelvic lymph node dissection (Neerhut *et al.*, 1988). Pathologically the operative specimen showed a poorly differentiated adenocarcinoma (Gleason score 8) with microscopic extracapsular extension. The surgical margins were negative. The histological sections showed a ductal adenocarcinoma of the prostate with central necrosis and dystrophic calcification within solid tumour nests, a pattern similar to that of comedo-carcinoma of the breast (Haagensen and Asch, 1981) (Fig. 2). The total tumour volume was 3.4 ml. When the sonographic images were compared with corresponding pathological sections, the hyperchoic areas corresponded to the areas of calcification (Fig. 1). The hypoechoic area on the right side proved to be an edge artifact. The patient died in February 1988 from a second primary small cell cancer of the lung.

Case 2. A 66-year-old man underwent transurethral resection of the prostate in 1981 for benign prostatic hypertrophy. Subsequent digital rectal examinations revealed a palpable nodularity, although digitally guided transrectal biopsies on 6 separate occasions were negative. Rectal examination revealed a firm and enlarged left lobe which was suspected to be prostate cancer. The right lobe was also granular and firm, and the clinical stage was judged to be B2 (both lobes involved). A digitally-guided needle biopsy revealed adenocarcinoma of the prostate (Gleason score 9). Metastatic evaluation was unremarkable. The pre-operative ultrasound with an Aloka SSD 520 chair-type radial scanner equipped with 7.0 MHz transrectal probe revealed a hyperechoic area in the left lobe and irregularity and convexity of the posterior aspect of the gland, suggesting extracapsular extension (Fig. 3A). Radical retropubic prostatectomy and bilateral lymph node dissection were performed in January 1986. The tumour was a ductal adenocarcinoma (Gleason score 9) with extension outside the prostate and a positive surgical margin. Comedo-like tumour nests exhibited central necrosis and dystrophic calcification (Fig. 4). The total tumour volume was 10.8 ml. Sonographically the tumour appeared hyperechoic, with smaller hypoechoic areas (Fig. 3). Thereafter, the patient under-

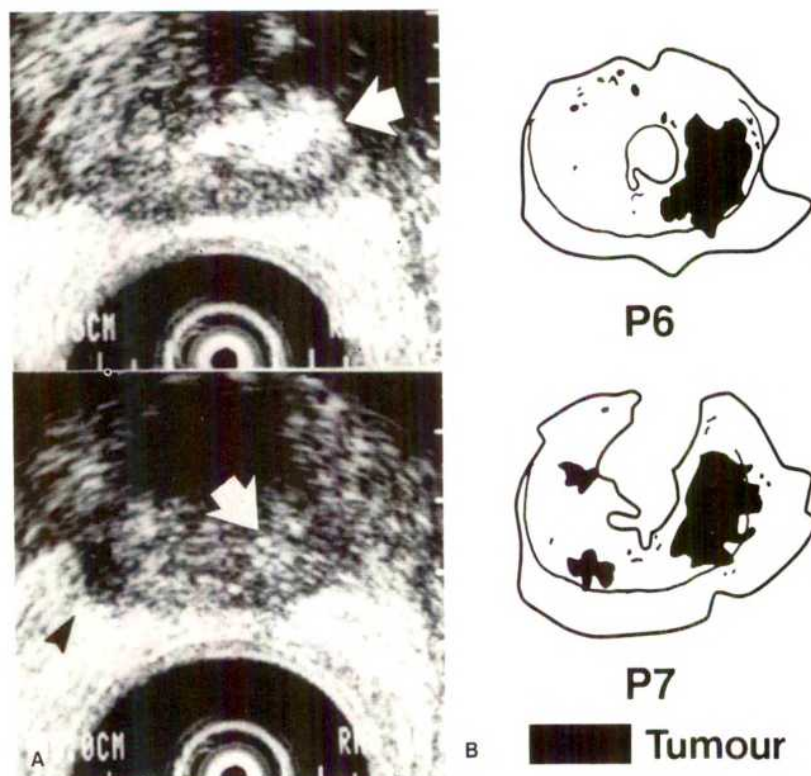


Fig. 1 Case 1. Hyperechoic tumour in an irradiated prostate gland. (A) Ultrasound scan, transverse image. A purely hyperechoic lesion is visible on the left side extending from the peripheral zone into the transition zone (arrow). A false positive hypoechoic lesion can be seen in the right peripheral zone (arrowhead). (B) Tumour maps of the prostate at the same levels as the sonograms.

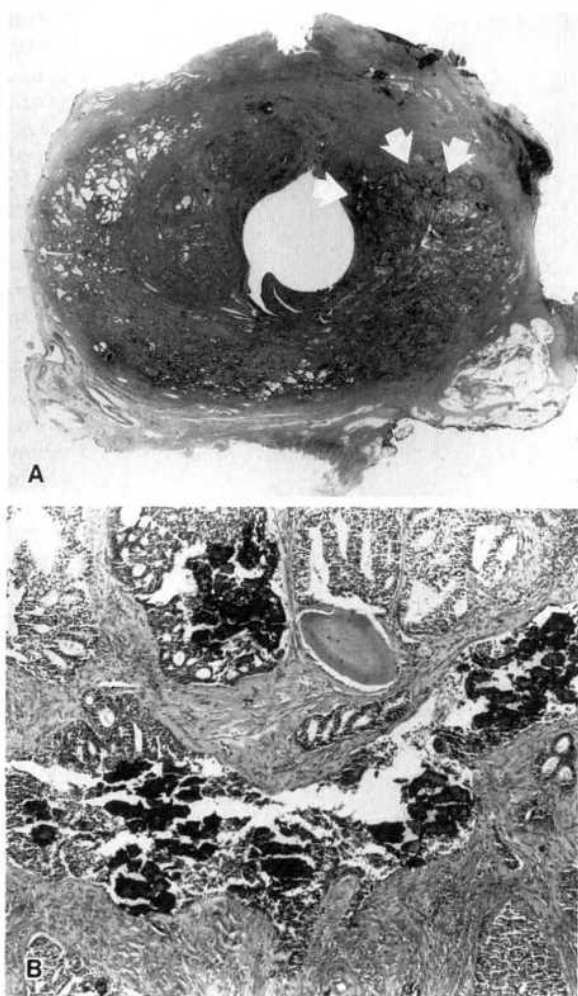


Fig. 2 Case 1. (A) Whole-mount step-section (corresponding to level P6 in Fig. 1B) showing tiny black dots, which represent calcifications within the tumour (arrows). (H and E, reduced from $\times 3.5$). (B) Histological section showing unusual ductal adenocarcinoma (Gleason score 8) with comedo-like necrosis and secondary calcification. (H and E $\times 62.5$).

went post-operative radiotherapy (6000 cGy) for local control; 44 months after surgery he remained free of disease.

Discussion

In the early experience with transrectal ultrasonography, prostate cancer was often reported to have a hyperechoic or echodense appearance (Resnick *et al.*, 1978; Rifkin *et al.*, 1983). With modern equipment and wider experience, most investigators have confirmed that the sonographic appearance of prostate cancer is characteristically hypoechoic (Lee *et al.*, 1985; Dähnert *et al.*, 1986a,b;

Griffiths *et al.*, 1987; Jones *et al.*, 1989; Shinohara *et al.*, 1989). Several studies have compared prostate sonograms with whole mount histological sections of radical prostatectomy or autopsy specimens, finding that 40 to 76% of prostate cancers appeared echopenic or hypoechoic, while 14 to 39% appeared isoechoic. A hyperechoic pattern (pure or mixed) has been observed with an incidence varying from 0 to 30% (Dähnert *et al.*, 1986a,b; Jones *et al.*, 1989; Shinohara *et al.*, 1989).

In a comparison of 49 radical prostatectomy specimens with sonograms obtained *in vivo* or *in vitro*, Dähnert *et al.* (1986a,b) found that none of the tumours appeared hyperechoic. Rifkin *et al.* (1989) recently reported that 10% of prostate cancers were subtly hyperechoic and 20% had a mixed echogenic pattern. They also reported that the echogenicity was correlated with stromal fibrotic changes or collagen content, although more than half of their pathological specimens were obtained by biopsy alone. In a previous study, Rifkin *et al.* (1986) also noted a few instances of acoustic shadowing from within an area of cancer, which they explained as calculi rather than malignancy. Jones *et al.* (1989), in an attempt to determine the echogenicity of prostate cancer using autopsy specimens, noted that 20% of 29 tumours appeared hyperechoic. The increased echogenicity was attributed to randomly distributed and irregularly shaped calcifications inside the tumours. No other histopathological features were found to be related to the hyperechogenicity of these tumours (Jones *et al.*, 1989). In our earlier study we found a predominantly hyperechoic pattern in only 1.4% of 70 instances in which serial transverse sonograms were compared with whole mount step-sections of radical prostatectomy specimens (Shinohara *et al.*, 1989).

There are a number of reasons for the various echogenic patterns of prostate cancer. These include the size, grade and location of the tumour (Shinohara *et al.*, 1989), desmoplastic reactions to the cancer (Rifkin *et al.*, 1989), the pattern of infiltration of cancer into normal tissue (Lee *et al.*, 1985; Shinohara *et al.*, 1989), and the presence of calcification within the tumours (Griffiths *et al.*, 1987; Jones *et al.*, 1989; Shinohara *et al.*, 1989). However, the apparent variation in the reported incidence of hyperechogenicity of prostate cancer seems to be related chiefly to the use of different (subjective) definitions of "hyperechoic" in the reported studies. Purely or predominantly hyperechoic tumours seem to be uncommon (none of 49 in the series of Dähnert *et al.*, (1986a) and 2 of 157 in the present series).

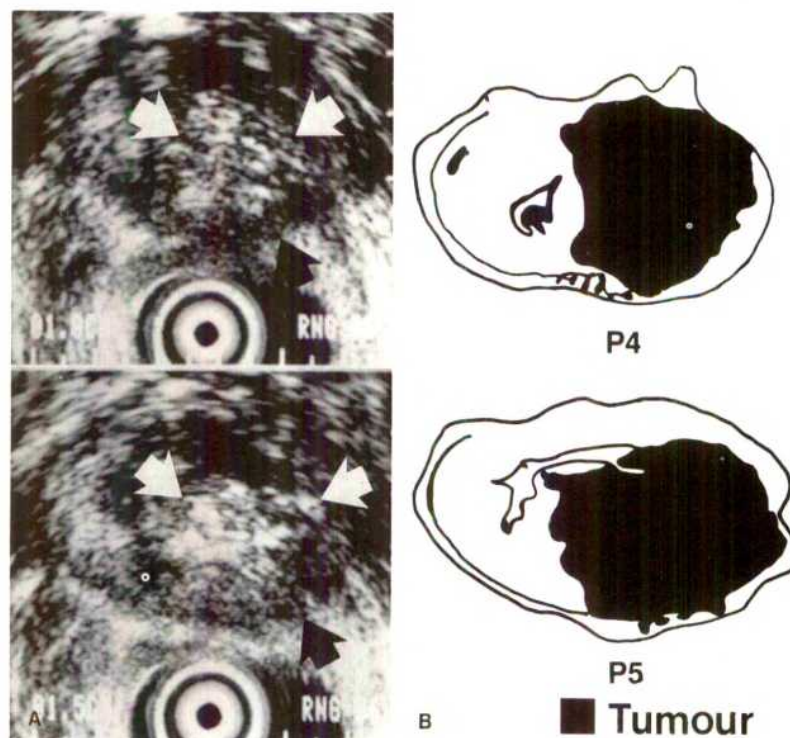


Fig. 3 Case 2. Predominantly hyperechoic tumour with some hypoechoic areas (mixed echogenic pattern). (A) Ultrasound scan, transverse image. Tumour of mixed echogenic pattern is visible in the left peripheral and transition zone posterolaterally with posterior convexity of the gland and irregularity of the overlying boundary echo (arrows). (B) Tumour maps of the corresponding histological sections.

The 2 hyperechoic tumours in our series were rare ductal adenocarcinomas with central necrosis and calcification. Foot *et al.*, (1950) proposed a classification for prostate cancers that recognised ductal type adenocarcinoma. Most adenocarcinomas within the peripheral zone of the prostate are made up of small glands which appear to arise from acini or peripheral ducts (Foot *et al.*, 1950; Dube *et al.*, 1973; Greene *et al.*, 1979; Wheeler, 1989). In a review of 4286 consecutive adenocarcinomas of the prostate, Dube *et al.* (1973) found that purely ductal adenocarcinomas accounted for only 1.3%, while mixed acinic and ductal adenocarcinomas made up 4.8% of the total cases. Prostatic adenocarcinomas of the ductal type are, therefore, uncommon. Ductal adenocarcinoma arising from the peripheral prostatic ducts has been shown to form comedo-like necrosis with many of the lumina filled with eosinophilic necrotic debris (Dube *et al.*, 1973; Greene *et al.*, 1979). This necrotic debris may undergo dystrophic calcification (Gibbs *et al.*, 1975; Kovi *et al.*, 1979).

Kovi *et al.* (1979) reported that calcification could be identified radiographically in 36% of 874

prostates sectioned at 4 mm and examined *in vitro*. Only 8% of these prostates contained invasive carcinoma. Distinct calcification was seen occasionally in invasive prostatic carcinoma. When calcification was seen within the carcinoma itself—which was rare—it was found within the necrotic material in the centre of composite glandular structures. They presented a figure illustrating calcification within the necrotic centre of a carcinomatous duct. In prostate glands with carcinoma and calcification, over 90% of calcifications were associated with benign acini or ducts and usually represented calcified corpora amylacea (Kovi *et al.*, 1979). Gibbs *et al.* (1975) found calcification in 5 of 23 prostate cancers (21.7%). Two of these were ductal carcinoma with fine basophilic granular calcification in the central portion of degenerated masses of malignant cells. The other 3 calcified cancers were microfollicular carcinoma which contained dense acellular eosinophilic secretion with a weak positive staining for calcium. In our series of 157 prostate cancers 2 other microglandular cancers exhibited calcification; 1 contained irregular intraluminal calcification and the other had

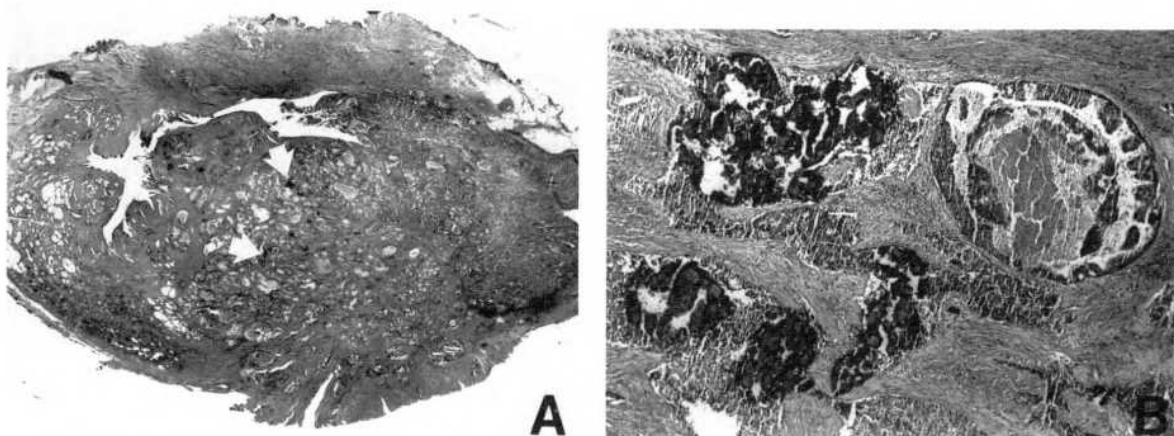


Fig. 4 Case 2. (A) Whole-mount step-section shows an extensive tumour. (H and E $\times 3.5$). The tiny black dots represent calcifications within the tumour (arrows). (B) Representative histological section of ductal adenocarcinoma (Gleason score 9) with comedo-like necrosis and secondary calcification (H and E $\times 62.5$).

psammoma bodies. Both of these tumours appeared hypoechoic sonographically. Microcalcifications are usually undetectable by ultrasonography unless many are packed closely together (Dähnert *et al.*, 1986b).

The most common cause of hyperchogenicity within the prostate is prostatic calculi, which are present in nearly 100% of men over 30 years of age (Horio, 1967). Prostatic calculi increase in number and tend to calcify with ageing. The strong echo reflections from prostatic calculi can be seen in about 80% of men during transrectal ultrasonogra-

phy of the prostate (Harada *et al.*, 1980). Prostatic calculi characteristically appear in a chain along the "surgical capsule" or the border between the transition zone and the peripheral zone (Harada *et al.*, 1980) (Fig. 5). Although calculi appear hyperechoic, their predictable anatomical location and regular appearance help to distinguish them from dystrophic calcification within prostate cancer (Jones *et al.*, 1989). Calcification within cancers has a more irregular pattern and sometimes extends across zonal boundaries, as in our cases, from the peripheral zone into the transition zone (Figs 1 and

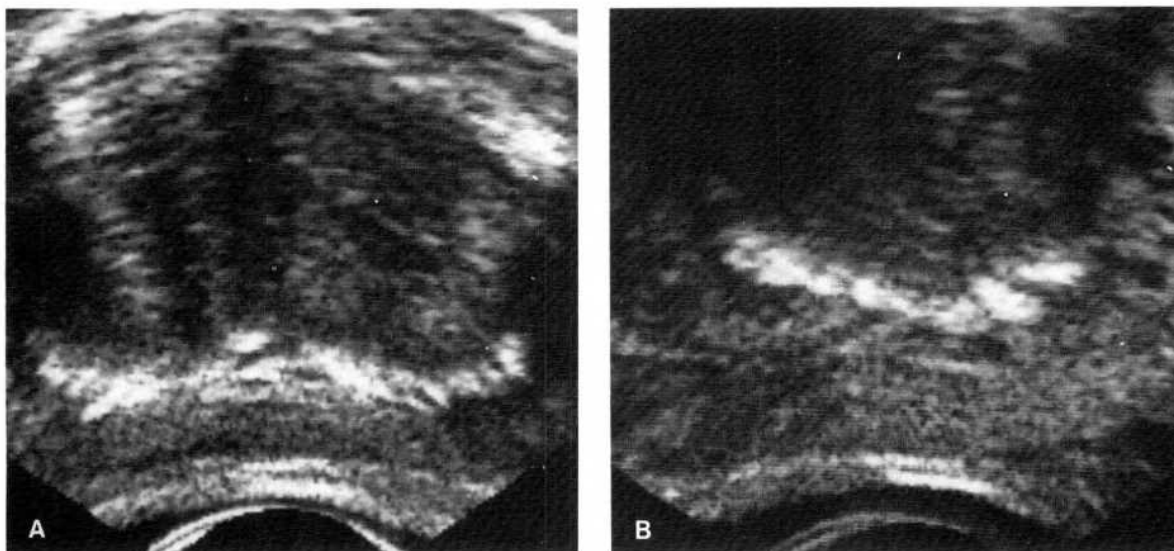


Fig. 5 Representative sonogram of the prostate showing multiple prostatic calculi. The calculi are densely echogenic and arranged in a chain along the border between the transition zone and the peripheral zone bilaterally. (A) Transverse image. (B) Longitudinal image.

3). Calcification seems to be associated with large tumours; in our 2 patients the total tumour volumes were 3, 4 and 10.8 ml.

The typical appearance of prostate cancer on transrectal ultrasonography is hypoechoic; hyperechoic cancers are rare. If a hypoechoic area surrounds or is adjacent to a hyperechoic focus, cancer should also be suspected. Other indirect signs of cancer, such as asymmetry of the peripheral zone (Watanabe *et al.*, 1975), irregularity or bulging of the overlying boundary echo, or gross distortion of the internal anatomy of the prostate (Scardino *et al.*, 1989) also suggest the presence of cancer. Such signs should be considered in the context of the other clinical findings, including the results of digital rectal examination and the level of serum markers (acid phosphatase and prostate specific antigen). Although most hyperechoic areas within the prostate are benign, the experienced sonographer should be alert to the occasional cancer which appears predominantly hyperechoic on ultrasonography.

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Prostate-specific Antigen and other Prognostic Factors in Patients with Hormone-resistant Prostatic Cancer Undergoing Experimental Treatment

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Summary—In 58 patients with progressive hormone-resistant metastatic cancer of the prostate, prostate-specific antigen (PSA) > 100 µg/l, haemoglobin < 12.0 g/dl and pronounced fatigue were found to be independent adverse prognostic factors. These risk factors distinguished a subgroup of patients with a median survival of 9 months (none or only 1 risk factor present) from a subgroup with a median survival of 4 months (≥ 2 risk factors present).

The clinician should be reluctant to enter patients from the second group into complicated and resource-demanding clinical studies, particularly if such trials require frequent and inconvenient follow-up examinations.

Urologists and medical oncologists sometimes consider experimental chemotherapy or hormone treatment in patients who have relapsed after primary hormone treatment. In addition, many patients, aware of their wide-spread disease, ask for systemic anti-cancer treatment. Such patients should principally be entered into phase II or phase III trials. Although such studies have undoubted scientific value, they require frequent follow-up visits which may be inconvenient for the patient and his family and are often expensive for the Health Service.

The aim of the present study was to define simple pre-treatment criteria which would predict survival in patients with hormone-resistant prostatic cancer who had received experimental systemic treatment. The objective was to identify prognostic factors which would justify a further trial of systemic treatment in patients with a favourable prognosis, as opposed to patients with a short survival who should probably not be entered into studies which require frequent, inconvenient and expensive follow-up visits.

Patients and Methods

Between December 1986 and September 1989, approximately 200 patients were referred to the Norwegian Radium Hospital (NRH) with hormone-resistant cancer of the prostate with metastases; 63 were given experimental hormone treatment or chemotherapy and 58 of these patients (Table 1) were eligible for the present study because they had had pre-treatment analysis of prostate-specific antigen (PSA).

All patients had symptomatic progression of their prostatic cancer and all had undergone orchiectomy or received LH–RH analogues. Twenty-five patients were entered into the EORTC trial 30865 (Newling *et al.*, 1990), comparing Estracyt (560–700 mg *per os* daily) with Mitomycin C (15 mg/m² intravenously every 6 weeks); 33 patients were entered into an institution-based phase II study evaluating flutamide 750 mg *per os* daily (Fosså *et al.*, 1990).

Criteria for eligibility included a WHO performance status of 3 or better (Miller *et al.*, 1981), serum testosterone within the castration level and the ability to keep frequent follow-up appointments.

Table 1 Details of Patients

No. of patients	58
Age (years)	68* (51–77)†
Months from initial diagnosis to trial entry	23 (5–145)
Previous radiotherapy (yes/no)	20/38
Trial treatment	
Estracyt or Mitomycin C	25
Flutamide	33
Bone scan‡	
0	1
1	5
2	10
3/4	41
Performance status (WHO)	
0/1	27
2	26
3	5
Use of analgesics	
No	8
Non-narcotics	29
Narcotics	21
Haemoglobin (g/dl)	12.1 (8.5–16.8)
Alkaline phosphatase (u/l)	518 (145–10,248)
Prostatic acid phosphatase (PAP) (u/l)	4.1 (0.2–198)
Prostate-specific antigen (PSA) (µg/l)	169 (2–3890)
Creatinine (µmol/l)	90 (54–250)
Questionnaire:	
Fatigue <3	36
≥3	22
Pain <3	17
≥3	39
Social life impairment <3	35
≥3	23

* Median. † Range. ‡ Scoring system according to Soloway *et al.* (1988).

§ Response alternatives: 1: Not at all; 2: A little; 3: Quite a bit; 4: Very much. The total number of alternatives may be less than 58 because of lack of answers.

The criteria did not include measurable disease. Time to progression was the essential end-point in EORTC protocol 30865, and subjective response was evaluated in the flutamide trial.

Before entry to the trial the following investigations were performed: blood cell count, serum creatinine (upper normal limit: 125 µmol/l), alkaline phosphatase (APHOS, upper normal limit: 270 u/l), prostatic acid phosphatase (PAP, upper normal limit: 1 u/l) and prostate-specific antigen (PSA, Hybritech, upper normal limit for the actual age group: 10 µg/l). A ⁹⁹Tc bone scan was done before entry to the trial. The result of the individual

bone scan was semi-quantitatively recorded according to the extent of the disease (EOD) as recommended by Soloway *et al.* (1988)—(0: no metastases; 1: 1–6 hot spots; 2: 7–20 hot spots; 3: >20 hot spots; 4: superscan). The patient's pain level was assessed by the doctor and scored according to the use of analgesics—(0: no analgesics; 1: non-narcotics irregularly; 2: non-narcotics regularly; 3: narcotics irregularly; 4: narcotics regularly).

In addition, the patients completed a self-administered questionnaire before starting treatment, assessing the type and degree of objective morbidity such as pain, fatigue and impairment of social life (Fosså *et al.*, 1989). The patients' answers were recorded according to a Likert scale—(1: not at all; 2: a little; 3: quite a bit; 4: very much).

Statistics

A PC-based statistical package "Medlog" was used to calculate medians, ranges, the Fisher exact probability test and the Wilcoxon rank test. Survival was estimated by the Kaplan-Meier method and survival differences were assessed by the Logrank test. Independent prognostic parameters were determined by the Cox regression multivariate analysis. A *P* value <0.05 was regarded as statistically significant.

Results

The median survival for all patients was 8.3 months from the start of treatment (Fig. 1). In univariate analyses the following parameters were significantly related to a poor prognosis: haemoglobin

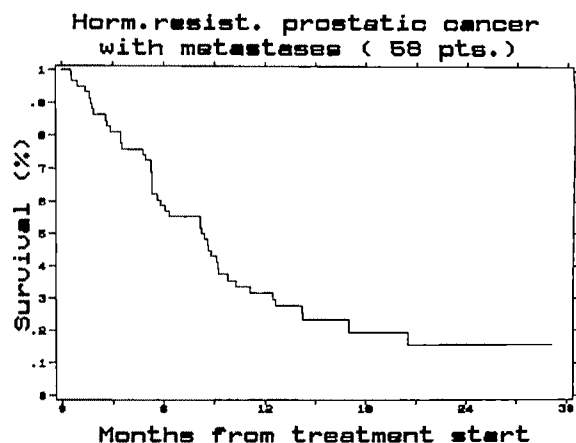


Fig. 1 Crude survival in 58 patients with hormone-resistant prostatic cancer entered into prospective clinical trials evaluating systemic hormone or cytostatic treatment.

(Hb) <12 g/dl, pronounced fatigue and impairment of social life (Table 2). The pre-treatment level of PSA, the performance status and the bone scan score represented almost statistically significant prognostic variables. The levels of initial alkaline phosphatase and prostatic acid phosphatase, and the degree of pain (assessed either by the doctor or the patient) did not influence survival. In the Cox regression analysis only haemoglobin, PSA and fatigue (as assessed by the patient) remained independent prognostic variables.

Haemoglobin and PSA were subsequently related to the patients' 6-month survival rate (Table 3). For those patients whose haemoglobin was ≥ 12.0 g/dl and PSA ≤ 100 μ g/l at entry to the trial, only 4 of 19 were dead within the first 6 months after entry, as opposed to 12 of 20 deceased patients whose haemoglobin was <12.0 g/dl and PSA >100 μ g/l ($P < 0.02$). Eight of 19 patients from an intermediate group were dead at 6 months. If pronounced fatigue was added as a third variable, 2 significantly different prognostic groups could be identified using the following high risk factors: Hb <12 g/dl, PSA >100 μ g/l, fatigue score ≥ 3 . In the absence of all of these risk factors or the presence of only 1, the 6-

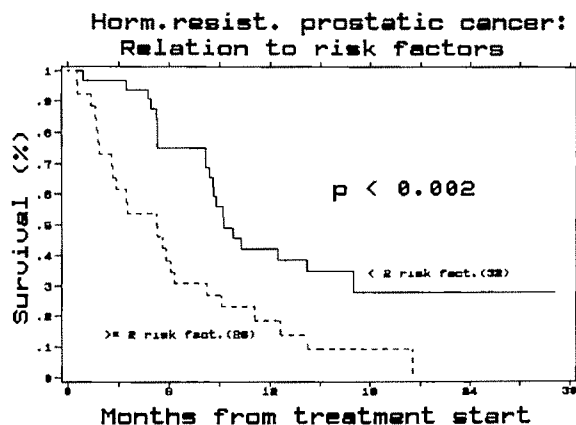


Fig. 2 Crude survival according to high risk factors (Hb <12.0 g/dl, PSA >100 μ g/l; pronounced fatigue) ($P < 0.01$). — none or only 1 high risk factor present (32 patients) - - - ≥ 2 risk factors present (26 patients).

and 12-month survival rates were 73 and 39% respectively. If at least 2 of these high risk factors were present, the 6- and 12-month survival rates were 37 and 14% respectively (Fig. 2) ($P < 0.01$).

Table 2 Results of Univariate Survival Analysis

Parameter	Cut-off level	P
<i>Objective parameters (doctor's assessment)</i>		
Age	70 years	0.23
Months from initial diagnosis	18/12	0.33
Performance status	≤ 1 vs ≥ 2	0.07
Bone scan	≤ 2 vs ≥ 3	0.11
Use of analgesics	≤ 2 vs ≥ 3	0.72
Haemoglobin	12 g/dl	0.01
Alkaline phosphatase	675 u/l	0.41
PAP	4 u/l	0.34
PSA	100 μ g/l	0.09
<i>Subjective parameters (patient's assessment)</i>		
Fatigue	<3 vs ≥ 3	0.003
Social life impairment	<3 vs ≥ 3	0.03
Pain	<3 vs ≥ 3	0.58

Table 3 Haemoglobin and PSA Versus Risk of Death within 6 Months after Entry to Trial

PSA (μ g/l)	Haemoglobin (g/dl)	
	≥ 12	<12
≤ 100	4/19*	3/7
>100	5/12	12/20

* Dead/all patients within the group.

Discussion

Only about 30% of all patients with hormone-resistant prostatic cancer seen at the uro-oncological unit at the NRH were entered into ongoing trials for systemic treatment. In general, the only patients eligible for phase II or phase III studies were those whose general condition allowed frequent follow-up visits. Our 58 patients thus represented a particularly favourable subgroup of all patients with hormone-resistant prostatic cancer.

Another criterion for eligibility was "symptomatic progression", most often pain resistant to the conventional use of analgesics. Subjective deterioration was, in fact, the most frequent reason for referral to the NRH. At that time the majority of patients had very advanced disease (assessed by bone scan, PSA and/or alkaline phosphatase), but individual features of progression (Beynon and Chisholm, 1984) could not be evaluated because of the frequent lack of pre-referral examinations. Although it is likely that subjective deterioration of the patient with hormone-resistant prostatic cancer is most often correlated with an objective increase in the tumour burden, there might be a few exceptions to this clinical experience.

The observation that pain, evaluated either by the doctor or the patient, had no influence on prognosis is surprising when viewed against the

background that pain has been shown to be an important prognostic parameter in newly diagnosed prostatic cancer (de Voogt *et al.*, 1989). This discrepancy may be due to difficulties in assessing pain in patients with hormone-resistant prostatic cancer. Many, but not all, patients in the present study experienced severe pain when they were included in the trial, despite ongoing analgesic treatment.

The doctor's method of scoring pain by simply recording the type of analgesic used, but not its effectiveness, therefore correlated more with the quality of analgesic treatment than with the patient's experience of pain. Furthermore, the question assessing pain in the patient's questionnaire was not clearly worded: it left some doubt as to whether the patient should score his pain while using the prescribed analgesics or whether he should try to assess his pain without taking pain killers. Probably because of these uncertainties and variations, evaluation of pain in the present study did not adequately mirror the metastatic tumour burden and was therefore not related to prognosis. On the other hand, Berry *et al.* (1979) reported that severe bone pain was significantly correlated with a short survival.

In previous untreated patients the extent of metastatic bone involvement seemed to be adequately mirrored by the scoring system first described by Soloway *et al.* (1988), which provided important prognostic information. In the present limited series its relevance was less, although the survival rate in patients with an EOD score ≥ 3 tended to be lower. After analysing our data we would also suggest a subdivision of bone scan score 2, discriminating between patients with 7 to 12 metastases and those with 13 to 20 hot spots. The extended use of the bone scan EOD scores as prognostic parameters in patients with hormone-resistant prostatic cancer may, however, be limited by the fact that skeletal scintigraphy is usually available only at larger hospitals.

In patients with newly diagnosed prostatic cancer the WHO performance status has been shown to be a significant prognostic factor (de Voogt *et al.*, 1989; Ishikawa *et al.*, 1989). Berry *et al.* (1979) and Paulson *et al.* (1979) confirmed this parameter for patients with hormone-resistant cancer of the prostate. However, in the present limited series this parameter had a lower prognostic impact. Fatigue, assessed by the patient himself, was a more accurate predictor. One reason may be that the performance status in patients with hormone-resistant prostatic cancer might be influenced to a higher degree by

the efficacy of analgesic treatment than is probably the case in previously untreated patients. Furthermore, in patients with hormone-resistant prostatic cancer the doctor's routine evaluation of their performance status does not always mirror the patient's own experience of decreased functional status (Fosså *et al.*, 1990).

PSA has been shown to be a powerful tumour marker in patients with prostatic cancer (Kuriyama *et al.*, 1981; Cooper *et al.*, 1990). High levels of PSA are correlated with a short survival. The clinical significance of PSA in patients with hormone-resistant prostatic cancer has been less well studied and PAP has usually been considered a relevant prognostic tumour marker (Berry *et al.*, 1979; Paulson *et al.*, 1979). The present study demonstrates an almost significant correlation between the pre-treatment PSA level and survival in patients with hormone-resistant prostatic cancer, whereas PAP could not be used as a prognostic factor. In this study the cut-off level for PSA (100 $\mu\text{g/l}$) was arbitrarily selected on the basis of distribution of PSA levels observed in our patients. The significance of this level has still to be tested in a larger series.

The main aim of the present analysis was to define simple parameters which would guide the clinician in deciding whether or not a patient should be entered into a phase II or phase III study for experimental systemic treatment, with all the inconvenience and use of resources that this may imply. This decision is of particular interest in countries where—as in Norway—patients sometimes have to travel long distances in order to reach larger hospitals where bone scans, computed tomography, *etc.*, are available. Many protocols for clinical trials require the repeated use of such examinations. Haemoglobin and PSA (but not PAP) were such objective prognostic parameters, thus supporting the suggestion by Ahmann and Schiffman (1987) that PSA is a "potentially more useful tumour marker than PAP measurements in patients with prostatic cancer with metastases". When the results of haemoglobin and PSA were combined and arbitrary cut-off levels were used (Hb: 12 g/dl; PSA: 100 $\mu\text{g/l}$), they significantly discriminated between 2 risk groups with regard to the 6-month survival rate, with an intermediate group between the low and high risk group. If pronounced fatigue was added as a third parameter, 2 different groups of patients could be identified with regard to overall survival.

Haemoglobin and PSA can easily be assessed in a blood sample taken at local hospitals or by the

general practitioner without referring the patient to a specialised hospital unit. Together with information on fatigue, these parameters may help the local doctor to decide on further management. These variables may also help to identify patients with a more favourable survival in whom experimental hormone or cytostatic treatment may be most feasible and justifiable. The doctor should probably be more reluctant to enter patients with a particularly short life expectancy into complicated and resource-demanding clinical trials.

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Detection of Lymph Node Invasion in Prostatic Carcinoma with Iliopelvic Lymphoscintigraphy

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Summary—Eleven patients, ranging in age from 58 to 79 years and referred for ^{125}I implantation because of localised prostatic carcinoma, were subjected to iliopelvic lymphoscintigraphy (IPL) prior to lymph node dissection. Scintigraphy was performed by perianal injection into the ischiorectal fossa of 0.2 ml $^{99\text{m}}\text{Tc}$ radio-labelled antimony sulphide colloid. The sensitivity of IPL was 100% and the specificity 13%, with a prevalence of positive nodes of 27%. It was concluded that IPL is not useful as a non-surgical method of detecting lymph node invasion in localised prostatic carcinoma because of the low specificity.

Patients referred for radical treatment of locally confined prostatic carcinoma are usually subjected to staging lymph node dissection, since this is the only reliable method of early detection of lymph node invasion to date. Lymphangiography and CT scan are known to be unreliable investigations. Early reports on the scintigraphic visualisation of pelvic lymph nodes in prostatic cancer were promising; unfortunately, the value of this method has been based largely upon clinical staging, as histopathological comparison has been done in only a small number of patients. We investigated the role of iliopelvic lymphoscintigraphy in detecting lymph node metastases in localised prostatic cancer, as the first phase of a project in which scintigraphic examination of radio-labelled monoclonal antibodies against prostatic cancer is assessed.

Patients and Methods

Eleven patients with localised prostatic carcinoma (age range 58–79 years) were subjected to IPL, prior to modified pelvic lymph node dissection (Whitmore, 1984) and retropubic ^{125}I implantation.

Iliopelvic lymphoscintigraphy was performed according to the method described by Ege (1982): 37 MBq (1 mCi) $^{99\text{m}}\text{Tc}$ radio-labelled antimony sulphide colloid in a volume of 0.2 ml was introduced into the ischiorectal fossa, by perianal injection at 3 and 9 o'clock, using a 22 gauge needle. The procedure was well tolerated. No prior preparation or local anaesthesia was necessary. Imaging was performed 3 h after injection, using a gamma camera. On the following day surgery was performed. Histopathology of the lymph nodes was compared with the results of scintigraphy, which was scored positive if node invasion was suspected, or negative if no sign of lymph node invasion was seen.

Results

Table 1 shows the distribution of T stage, the final outcome of lymph node dissection and the findings of iliopelvic lymphoscintigraphy. Table 2 shows the relation between the outcome of histology and iliopelvic lymphoscintigraphy. With a prevalence of 27% positive nodes, the sensitivity of IPL was 100% but the specificity only 13%.

There were no complications as a result of IPL.

Table 1 T stage and Outcome of Lymph Node Dissection and Iliopelvic Lymphoscintigraphy

Stage	Lymph node dissection	IPL
T2	—	+
T1	—	+
T2	—	+
T0	—	+
T2	+	+
T2	+	+
T0 ¹	—	+
T1	—	—
T2 ¹	+	+
T1 ¹	—	+
T2 ¹	—	+

Table 2 Relation between Histology of Lymph Nodes and Results of Iliopelvic Lymphoscintigraphy

	IPL positive	IPL negative	Total
pN ⁺	3	0	3
pN ⁻	7	1	8
	10	1	11

Sensitivity 100%.

Specificity 13%.

Prevalence of positive nodes 27%.

Discussion

Accurate staging of the lymph nodes is indispensable in the management of locally confined prostatic carcinoma and surgical lymph node dissection remains the most reliable means of assessment, since non-surgical methods are not sufficiently accurate. Successful scintigraphic visualisation of the lymphatic drainage of the prostate by radiocolloid injection has been reported (Gardiner *et al.*, 1979; Stone *et al.*, 1979; Kaplan *et al.*, 1980; Whitmore *et al.*, 1980). A more general method of assessing the lymph nodes in patients with neoplasms arising from pelvic organs was developed using bilateral deep perianal injection of radiocolloid into the ischio-rectal fossa, providing visualisation of pararectal, obturator, internal iliac, presacral, common iliac and para-aortic lymph nodes (Ege and Cummings, 1980). We have adopted this method because of its ease and reported consistency (Ege, 1982). The normal IPL image demonstrates a relatively symmetrical and uniform sequence of well delineated foci of radiocolloid accumulation, indicating patent lymphatic channels and grossly intact lymph nodes.

Scintigraphic manifestation of lymph node invasion is the result of obstructed lymph flow or reduced retention capacity of the lymph node resulting in an obvious discrepancy in the relative symmetry of non-lymphatic visualisation (Ege *et al.*, 1980) (Fig.).

In a study of 42 patients with primary gastrointestinal cancer, a histopathological comparison with IPL was available. The sensitivity and specificity were 70 and 55% respectively (Ege *et al.*, 1980). IPL in our experience visualised only a short section of the pelvic lymphatic pathways.

The average prevalence of lymph node metas-

tases in T1 and T2 prostatic cancer, independent of grade, is approximately 20%. With a specificity of 13%, the predictive value of a positive IPL, with a prevalence of 20% positive nodes, is only 25%.

Thus a positive IPL does not substantially increase the likelihood of lymph node metastases. The predictive value of a negative test, with a sensitivity of 100% and a prevalence of 20% positive nodes, is 82%. While the sensitivity was very high in the present series, no conclusions can be drawn from this because of the small number of patients.

It was concluded that IPL with ^{99m}Tc labelled radiocolloid is not useful as a non-surgical method of detecting pelvic lymph node invasion in localised prostatic carcinoma, because the specificity and

**Fig.** Positive iliopelvic lymphoscintigraphy. Asymmetrical visualisation of pelvic lymph nodes.

predictive value of a positive test are too low to be clinically useful.

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Deferred Treatment in Clinically Localised Prostatic Carcinoma

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Summary—A series of 122 patients with a cytological diagnosis of well or moderately differentiated and clinically localised (T1–2) prostatic carcinoma were followed up without any initial anti-tumour therapy. The median observation time was 91 months. During follow-up the local tumour progressed to stage T3 in 67 patients (55%) and distant metastases developed in 17 (14%); 47 patients died (38%), 9 of them (7%) from prostatic carcinoma. The risk of dying from prostatic carcinoma was 1% after 5 years and 16% after 10 years for patients not dying from other causes.

The natural course of localised prostatic carcinoma is not yet known. Whitmore (1984) found long survival times even without progression in a selected group of patients with stage B (T1–2) prostatic carcinoma subjected to deferred treatment. We have previously reported a small number of patients who progressed with metastases after 5 years' observation in a group of patients with T1–3, low-grade, non-metastatic prostatic carcinoma receiving no initial anti-tumour therapy (Adolfsson *et al.*, 1990). The number of patients whose death was due to prostatic carcinoma was also found to be small. Follow-up has now been extended and was made 10 years after the first patients were included. An analysis of the subgroup of patients with clinically localised (T1–2) tumours is now presented.

Patients and Methods

Between 1978 and 1982, 172 patients with newly detected low grade prostatic carcinoma were prospectively included in a surveillance study. Most patients had small tumours but those with larger tumours who were reluctant to accept therapy were also included. The patients were selected from a larger group of patients. No formal variables were

used in the selection and no randomisation was performed. All carcinomas were cytologically diagnosed on material obtained by transrectal fine needle aspiration biopsy. The tumours were graded according to the criteria described by Esposti (1971). Only patients with well or moderately differentiated tumours were included in the study. Local tumour stage was assessed by digital rectal examination (DRE) and the tumours were categorised according to the TNM classification (UICC, 1978). The DRE finding was recorded by means of a standard drawing and a statement in the patient's case notes. The status of metastases was assessed by radioisotope scanning of the skeleton (bone scan) and serum acid phosphatase was measured with a tartrate-inhibited enzymatic assay. All patients had a normal bone scan and a normal value of serum acid phosphatase and were regarded as without metastases (M0). The patients were followed up by routine clinical investigation and serum acid phosphatase every third to sixth month. Bone scan was performed routinely in all patients every 12 to 18 months. If rapid local progression or development of metastases was noted, anti-tumour therapy was given. Local progression was defined as a $\geq 25\%$ increase in the diameter of the tumour as judged from the standard drawings and statements in the case notes. Progression of the local tumour to stage T3 was also recorded and this information was used

in the analysis. A positive bone scan or plain X-ray was required to define progression with metastases. Cause and time of death were obtained from the case notes and from the National Swedish Death Register. Death from prostatic carcinoma was defined as death after a previous systemic progression with subsequent clinical deterioration followed by death. Patients dying of uraemia secondary to ureteric obstruction from local tumour growth were also included in this category. Death from intercurrent disease was defined as death from disease not related to prostatic carcinoma as recorded in our own files or files from the hospital where the patient died. Patients dying at home in whom no systemic progression had been documented and where the death certificate indicated a cause of death not related to prostatic carcinoma were also considered as having died from intercurrent disease.

In 122 of the 172 patients the tumour was categorised as localised within the prostatic capsule (T1–2) at diagnosis and the records of these patients were reviewed in September 1989. No patients were lost to follow-up. The 50 patients with clinically non-localised tumours (T3) were reviewed separately (unpublished data).

The prognostic value of the different variables determined at the time of diagnosis was analysed using Cox's proportional hazards regression model

(Cox, 1972). Rate ratios were estimated as e^{β} and 95% confidence intervals as $e^{\beta \pm 1.96 \times SE}$, where β is the regression coefficient of the Cox model and SE the standard error of the regression coefficient. The cumulative probability of not progressing was estimated and plotted using the actuarial method described by Berkson and Gage (1950). The patients who died from intercurrent disease were also included in the analysis but were considered as censored data.

The median age at diagnosis was 68 years (range 38–89) and median observation time was 91 months (range 8–127). In 13 patients the tumour was categorised as T1 and in 109 as T2. The tumour was well differentiated in 77 patients and moderately differentiated in 45.

Results

In 67/122 patients (55%) the tumour had progressed to clinical stage T3. Cytological grade was of prognostic importance regarding progression to T3 when analysed together with local stage in a Cox's multivariate analysis (Table 1). The patients with T2 tumours had a tendency to progress to stage T3 earlier than those with T1 tumours but this difference was not statistically significant (Table 1).

In all, 17/122 patients (14%) progressed with

Table 1 Prognostic Value of Cytological Grade and Tumour Stage

Variable category	T3 (67)		M1 (17)	
	Rate ratio	95% confidence interval	Rate ratio	95% confidence interval
Grade				
Well differentiated (77)	1.0	—	1.0	—
Moderately differentiated (45)	1.9	1.2–3.1*	1.2	0.4–3.2
Tumour stage				
T1 (13)	1.0	—	1.0	—
T2 (109)	1.5	0.6–3.6	1.0	0.2–4.5

* $P < 0.05$.

Numbers in parentheses are numbers of patients.

Table 2 Patients' Progress during Follow-up

	M1	Dead from prostatic carcinoma	Dead from intercurrent disease	Alive
5 years	9	2	21	99
At follow-up	17	9	38	75

metastases during follow-up (Table 2). Thirteen of these patients developed metastases before treatment and 4 after treatment had commenced. Neither grade nor stage had any significant prognostic importance regarding progression with metastases (Table 1). During follow-up 47 patients (38%) died, 9 (7%) from prostatic carcinoma and 38 (31%) from disease not related to prostatic carcinoma (Table 2). Of the patients who died from prostatic carcinoma 8 died after systemic progression followed by clinical deterioration and 1 died of uraemia secondary to ureteric obstruction due to local growth of the tumour. The number of deaths related to prostatic carcinoma was too small to permit a Cox analysis.

When the patients who died from intercurrent disease were censored in the analysis, the risk of developing metastases for patients alive at 5 and 10 years was found to be 8 and 28% respectively (Table 3) (Fig. 1). Similarly, the risk of dying from prostatic carcinoma was 1% after 5 years and 16% after 10 years (Table 3) (Fig. 2).

At the time of the review a total of 55 patients (45%) had been treated because of local and/or distant progression of their prostatic carcinoma. Such progression occurred at a steady rate throughout the observation period and there was no subgroup of patients with early rapid progress (Figs 1 and 2). At the time of follow-up, endocrine treatment had been given to 36 patients, 12 had received external radiation therapy to the prostate, 3 had been implanted with ^{125}I seeds and 4 had been subjected to radical prostatectomy.

Discussion

Two series on deferred treatment of localised prostatic carcinoma have been published. George (1988) reported 120 patients with clinically localised prostatic carcinoma of all grades. The median follow-up time was not given but is assumed to have been approximately 4 years since the patients were included in the study between 1980 and 1986, and follow-up probably took place during 1987.

Table 3 Probability of Progression

	<i>Progression to T3</i>	<i>M1</i>	<i>Death from prostatic carcinoma</i>
5 years	0.52 ± 0.05	0.08 ± 0.03	0.01 ± 0.009
10 years	0.69 ± 0.05	0.28 ± 0.09	0.16 ± 0.07

Values are means $\pm$ SE

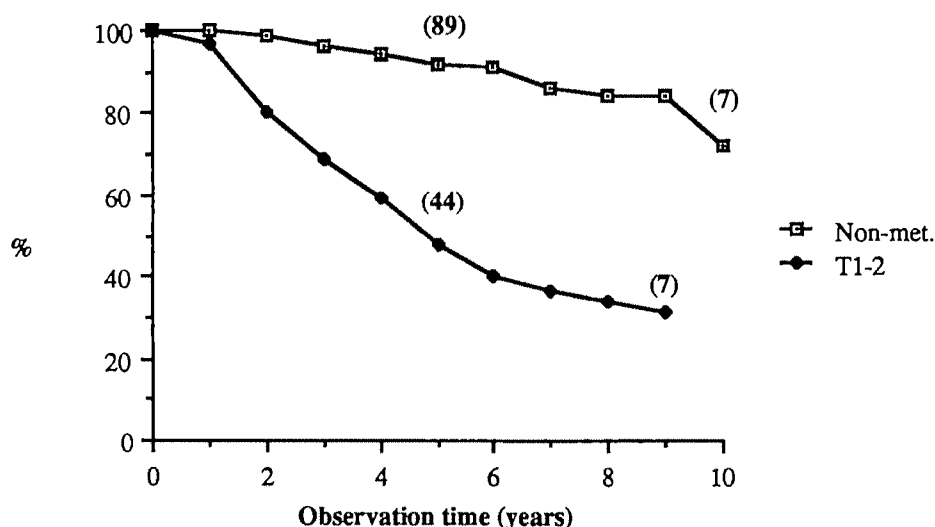


Fig 1 Relative number of patients with localised low-grade prostatic carcinoma remaining stage T1-2 and non-metastasized during the follow-up period (median 7.5 years). Numbers in parentheses are number of patients at risk.

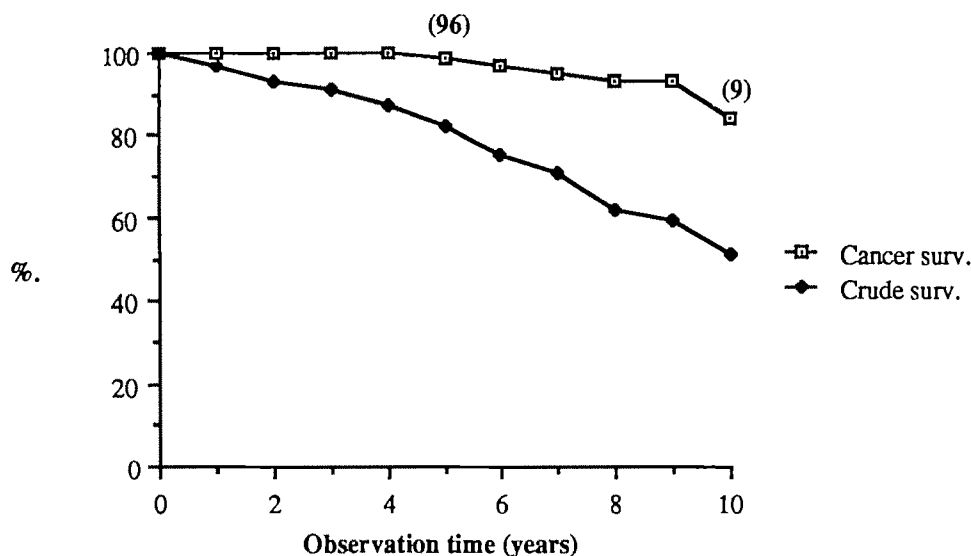


Fig. 2 Relative crude survival of patients with localised low-grade prostatic carcinoma and relative survival when patients dead of intercurrent disease have been censored from the analysis. Median follow-up period = 7.5 years. Numbers in parentheses are number of patients at risk.

Johansson *et al.* (1989) reported 223 patients with T0–2 tumours of all grades (9 patients with poorly differentiated tumours) with a mean follow-up of 6.5 years. In the present series, 122 patients with T1–2, well or moderately differentiated prostatic carcinomas were followed up for a median period of 7.5 years. In most patients the tumour seemed to progress locally with time. George (1988) reported a local progression rate of 84%, and in the present series 55% progressed to stage T3. We found that the cytological grade of the tumour had a prognostic value for progression to stage T3. There was a tendency for T2 tumours to progress faster than T1 lesions. The difference was, however, not statistically significant and this was probably due to the low number of patients with T1 tumours. The lower local progression rate in the present series may be explained by the selection of patients with well and moderately differentiated tumours. George (1988) also included patients with poorly differentiated tumours and these can be expected to progress at a higher rate, as shown by Esposti (1971). Local progression by itself is difficult to evaluate and compare between different investigators because of variations in the criteria used to evaluate this parameter.

In the series of George (1988), 13 patients developed metastases during the observation period. This represents 12% (13/105) of the eligible patients (105 patients, since 15 patients were not

followed up with bone scans). Johansson *et al.* (1989) reported that 9% of their patients (20/223) developed metastases and in the present series the corresponding rate was 14% (17/122). The slightly higher rate in this series may be due to the longer observation time.

With regard to the survival of patients with localised prostatic carcinoma, Whitmore (1984) reported long follow-up times even without progression in a group of patients with stage B (T1–2) tumours. This finding is supported by the findings of both the present and the studies of George (1988) and Johansson *et al.* (1989). Of our 122 patients with localised prostatic carcinoma, 47 (38%) had died at the time of follow-up and only 9 (7%) had died from prostatic carcinoma. The finding that the majority of the deaths were due to unrelated disease is consistent with the studies of George (1988), who reported 52 deaths (43%), of which 5 (4%) were from prostatic carcinoma, and Johansson *et al.* (1989), who reported 83 deaths (37%), of which 16 (7%) were from prostatic carcinoma.

The rates of metastatic and fatal disease which we found were influenced by the fact that many patients died from intercurrent disease during the observation period. If those patients who died of intercurrent disease during follow-up were treated as censored observations in the analysis, the rate of metastatic and fatal disease remains as shown in Figures 1 and 2. Therefore, according to our results,

the risk of developing metastases for the patients who were alive at 5 years was 8% and 28% at 10 years. Similarly, for patients not dying of any other disease, the risk of dying of prostatic carcinoma would be 1% before 5 years and 16% before 10 years. Owing to the high rate of intercurrent deaths, however, the risk of dying from any cause during the observation period (median 7.5 years) was 38% for the patients in the present study. The difference between the risk of dying from prostate cancer when deaths from intercurrent disease have been censored and the risk of dying from any cause represents the intercurrent mortality in the series, as illustrated in Figure 2.

In our previous report we concluded that patients with prostatic carcinoma subjected to deferred treatment progressed slowly during the first 5 years of observation (Adolfsson *et al.*, 1990). When comparing the extended follow-up of our patients with localised disease with the reports of George (1988) and Johansson *et al.* (1989), the natural course of localised, low grade prostatic carcinoma seems to be a slow but steady local progression with a low rate of metastatic disease and an even lower rate of fatal disease within the first 10 years after diagnosis. The risk of dying from intercurrent disease seems to be considerably higher than the risk of dying from prostatic carcinoma for this category of patients.

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Chronic Testicular Pain following Vasectomy

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Summary—The incidence of chronic testicular pain following vasectomy has not been previously assessed. We have carried out a survey by postal questionnaire and telephone interview of 172 patients 4 years after vasectomy to assess the incidence of chronic testicular pain. Significant early post-operative complications occurred in 6 patients (3.5%): 2 infection, 3 haematoma and 1 orchitis. Chronic testicular discomfort was present in 56 patients (33%), considered by 26 (15%) to be troublesome but not by the other 30 (17%). Testicular discomfort related to sexual intercourse occurred in 9 cases (5%). Of the 9 patients who had sought further medical help only 2 had had further surgery (1 an epididymectomy and 1 excision of a hydrocele). Only 3 patients regretted having had the vasectomy because of chronic pain. On ultrasound examination, epididymal cysts were a common finding on both asymptomatic and symptomatic patients following vasectomy. Prior to vasectomy, all patients should be counselled with regard to the risk of chronic testicular pain.

Vasectomy became accepted as a method of contraception in the 1950s and has become, after circumcision, the commonest operation performed in men. Chronic testicular pain is a recognised complication of vasectomy (Shapiro and Silber, 1979; Selikowitz and Schned, 1985) but the natural history and incidence of this problem are unknown. Indeed, it may not be widely recognised: several reported series of complications arising from vasectomy make no reference to chronic testicular pain (Barnes *et al.*, 1973; Esho *et al.*, 1973; Philp *et al.*, 1984). We are not aware of any reported series which have included follow-up of patients following vasectomy with particular reference to chronic testicular pain. Testicular pain after vasectomy is occasionally the subject of litigation, especially if the patient has also suffered post-operative complications such as haematoma. The aetiology of the pain is uncertain but might be related to fluid accumulation and cystic changes in the epididymis.

We report a survey 4 years after vasectomy to assess the incidence of chronic testicular pain.

Possible correlation with early complications or with ultrasonic abnormalities of the epididymis or testis has been investigated.

Patients and Methods

The study group consisted of 253 patients who had undergone vasectomy at the Glasgow Family Planning Centre between January and July 1986. All patients were sent a postal questionnaire (Fig.) in November 1990 (4 years after vasectomy). Those who failed to reply, and those who gave positive replies, were interviewed by telephone. Of the 253 patients, 72 had moved house and could not be traced and are unlikely to have received their questionnaire. A further 9 patients failed to reply and could not be contacted by telephone, leaving 172 (68%) who were assessed. The median age of the patients was 34 years (range 25–55). All but 2 of the operations were performed under local anaesthesia. The operative technique included ligation of proximal and distal ends of the vas deferens in all cases.

In addition, patients were invited to undergo testicular ultrasound; this was carried out in 14 patients who complained of chronic testicular

1. Are you aware of any difference in intercourse since your operation?		
Yes	[]	No []
2. Do you get any discomfort in the penis or the testicles before, during or after intercourse?		
Yes	[]	No []
3. A few men who have had vasectomies find that they get occasional discomfort in the testicles.		
Do you—	Never have any discomfort in the testicles	[]
	Get occasional discomfort which does not trouble you	[]
	Have occasional discomfort which is a nuisance	[]
	Have pain in the testicles which is bad enough to affect your way of life	[]
4. Do you ever experience any swelling in or behind the testicles?		
No	[]	
Yes—occasionally	[]	
Yes—frequently	[]	
Yes—permanently	[]	
5. If you have had pain or swelling following your operation please indicate how long after the operation you first noticed it:		
Pain	_____	
Swelling	_____	
6. Would you be prepared to attend the Western Infirmary for an ultrasound scan of your testicles?		
Yes	[]	No []

Fig. Postal questionnaire.

discomfort and in 13 patients who had not had prolonged discomfort or any complications related to vasectomy. Ultrasound was performed by a single operator (A.T.) using an "Acuson 128" computed sonography machine employing a 7.5 MHz linear array transducer.

Results

Only 6 (3.5%) of the 172 patients recalled significant early post-operative complications (taking more than a week to resolve): 2 developed wound infections, 1 of which was minor and resolved within 10 days, but the other was severe and required several courses of antibiotics, taking 18 weeks to settle; 3 developed scrotal haematomas which took 3 weeks, 4 weeks and 8 weeks to resolve with conservative management; 1 patient developed "orchitis" (GP's diagnosis) which resolved after antibiotic treatment. Of these 6 patients, 3 developed chronic testicular discomfort, which was troublesome in 2 cases.

A total of 56 patients (33%) had chronic testicular discomfort (predominantly unilateral): 26 of these (15%) considered the discomfort to be troublesome, while 30 (17%) did not. In the majority of cases the pain was intermittent and unilateral. In some the discomfort was a "dull ache" and in others it was a "sharp severe pain". Of these patients with chronic testicular discomfort, 11 (6%) also had "swelling in the scrotum". Testicular pain or discomfort at the time of intercourse occurred in 9 patients (5%), of whom 7 also had testicular discomfort at other times.

Only 9 patients (5%) had sought further medical help for chronic testicular pain or swelling. Two had seen their general practitioner without any further action being taken—in both cases the discomfort settled after 3 years; 4 patients had been referred to a consultant surgeon, without any further action being taken; 2 had undergone further surgery: 1 had had an epididymectomy performed for chronic testicular pain (without any benefit) and 1 had had repair of a hydrocele which had pre-

dated the vasectomy (with some improvement in the pain). As a result of this survey 2 patients have sought further treatment for chronic testicular pain (1 had previously seen a consultant but treatment was not recommended).

Only 2 patients regretted having had the operation (1 because of chronic testicular pain and the other because of a change of mind regarding further children), while 2 patients had reservations about the operation but did not regret it (both because of chronic testicular discomfort). Only 1 patient had undergone reversal of vasectomy.

Ultrasound examination of the scrotum was performed in 27 patients who had undergone vasectomy (14 with chronic testicular discomfort and 13 with no symptoms). Of the 14 patients who had chronic testicular discomfort, the ultrasound examination was normal in 7, while 4 had multiple bilateral epididymal cysts and 3 had unilateral epididymal cysts (in 2 of these cases the pain was on the opposite side). Of the 13 asymptomatic patients, the ultrasound examination was normal in 9, while 2 had bilateral epididymal cysts, 2 had unilateral epididymal cysts, and 1 had an atrophic hypoechoic testis. The majority of cysts were located in the head of the epididymis.

Discussion

Obstruction of the vas deferens results in a build-up of pressure, causing epididymal engorgement and epididymal blow-outs, which have been demonstrated at re-operation for reversal of vasectomy (Shapiro and Silber, 1979) and by sequential ultrasound (Jarvis and Dubbins, 1989). It is therefore not surprising that a percentage of patients develop chronic testicular discomfort. This study has demonstrated that mild chronic testicular discomfort is a common sequel of vasectomy. Pain or discomfort troublesome enough to make the patient seek further treatment and to regret vasectomy is, however, uncommon (5%). These findings have important implications for informed consent: perhaps all patients should be warned of this complication before vasectomy. Although half of the patients who reported post-operative complications had long-term discomfort, there was no obvious relationship with immediate post-operative problems such as bleeding, haematoma or infection (which patients may deem to be due to surgical negligence); this has important medico-legal implications.

Various terms have been used to describe this

syndrome: late post-vasectomy syndrome (Selikowitz and Schned, 1985), post-vasectomy orchialgia (Shapiro and Silber, 1979), congestive epididymitis (Schmidt and Free, 1979) and post-vasectomy pain syndrome (McCormick and Lapointe, 1988). Selikowitz and Schned (1979) described in detail a series of 18 patients with chronic testicular pain following vasectomy. The pain was unilateral in 16 and bilateral in 2. They were all seen 5 to 7 years after vasectomy for unremitting epididymal pain and induration which had failed to respond to conservative measures. The patients had been referred to them over a 2-year period. Seventeen of these 18 patients were treated by epididymectomy with complete relief of pain in all cases. Histology of the epididymis showed dilated tubules packed with sperm, and ruptured tubules with extravasation of sperm, granuloma formation and haemosiderin deposition. Shapiro and Silber (1979) reported 9 patients with chronic testicular pain following vasectomy. All had severe epididymal swelling and tenderness, aggravated by sexual intercourse and ejaculation. The pain was unilateral in 3 cases and bilateral in 6. In 2 of the patients the pain was relieved by excision of a sperm granuloma. In 6 patients (who did not have sperm granulomas) pain was relieved by vasovasostomy.

While sperm granulomas are very common, occurring in about a third of patients after vasectomy (Silber, 1977), painful granulomas requiring excision are rare, occurring in 0.5% of patients (Schmidt and Free, 1979). None of the patients in the present series required excision of a sperm granuloma.

Our ultrasonic findings are similar to those of the only previous ultrasound study after vasectomy. Jarvis and Dubbins (1989) prospectively evaluated the sonographic appearance of the testis and epididymis before, 2 months and 1 year after vasectomy in 31 patients. They found enlargement of the epididymis in 14 patients (45%) but this resolved by 1 year in 9 patients. Small pre-existing cysts 3 mm in diameter were present in 6 patients (19%) but new epididymal cysts developed in 17 patients (none of their patients had any long-term symptoms).

In conclusion, a third of vasectomy patients develop chronic testicular discomfort but only a few develop more severe pain that requires further surgical treatment. Informed consent needs to take account of this finding. Ultrasound frequently demonstrates epididymal cysts in vasectomised patients, both in asymptomatic patients and in those with chronic pain.

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PAEDIATRIC UROLOGY

Testicular Function in Patients with Hypospadias Associated with Enlarged Prostatic Utricle

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Summary—Of 485 patients with hypospadias who underwent urethrography, enlarged prostatic utricles were found in 173 (35.7%). Utricles with a higher grade of enlargement were seen mainly in patients with a severe degree of hypospadias. Serum testosterone levels before and after 3 days' treatment with human chorionic gonadotrophin were determined by radioimmunoassay in 97 prepubertal boys with hypospadias and enlarged prostatic utricles. Lower levels of serum testosterone were found after hormonal stimulation in 22 patients with high grade utricular enlargement when compared with 5 controls and 75 patients with low grade enlargement; the difference was statistically significant. This finding supports the hypothesis that utricular enlargement may be due to androgenic insufficiency during the critical period of organogenesis.

The prostatic utricle is a rudimentary structure present in the male prostatic urethra. It is thought to be of mixed origin, with its cranial portion derived from the müllerian duct and its caudal segment from the wolffian and müllerian ducts and the urogenital sinus (Glenister, 1962). Enlargement of the prostatic utricle has often been demonstrated in patients with hypospadias, and its incidence increases according to the severity of hypospadias (Howard, 1948; Shima *et al.*, 1979; Ikoma *et al.*, 1985). It has been suggested that insufficient androgenic stimulation of the urogenital sinus and urethral groove during the critical period of sexual differentiation may cause this entity (Devine *et al.*, 1980; Gonzalez-Serva *et al.*, 1981; Ikoma *et al.*, 1985).

The aim of this study was to investigate the response of testosterone to stimulation by human chorionic gonadotrophin (hCG) in patients with hypospadias associated with an enlarged prostatic utricle.

Patients and Methods

A total of 528 patients who were surgically treated

for hypospadias between 1973 and 1987 were reviewed with regard to the presence of an enlarged prostatic utricle; 485 of these patients underwent retrograde urethrocystography and/or micturition cystourethrography. The prostatic utricles visualised on urethrography were classified by a new radiological grading system (Ikoma *et al.*, 1985). Grade 0 indicates a utricle which does not extend over the verumontanum. A Grade I utricle extends over the verumontanum but does not reach the bladder neck. A Grade II utricle is more enlarged and its dome extends over the bladder neck.

In rare cases, the opening of the utricle is located in the bulbous part of the urethra. This type is classified as Grade III regardless of the size.

Testosterone levels in 97 patients with hypospadias associated with an enlarged prostatic utricle were examined after 3 days' consecutive stimulation by hCG according to the method described by Shima *et al.* (1986). The patients ranged in age from 2 to 8 years (mean 4). Blood was sampled every 24 h until 120 h had elapsed since the first intramuscular injection of the gonadotrophin. The maximal levels of serum testosterone after stimulation by hCG in these patients were compared with those of endocrinologically normal boys within the same age range (mean age 5.2 years).

Intersex patients, including mixed gonadal dysgenesis, were excluded from this study.

All values are expressed as the mean $\pm$ standard error of mean. Statistical difference was estimated by Student's unpaired *t* test.

Results

The degree of hypospadias in 528 patients is shown in Table 1; 173/485 patients (35.7%) with hypospadias had an enlarged prostatic utricle and the incidence increased in proportion to the severity of hypospadias (Table 2). Higher grade utricles (Grades II and III) were mainly seen in patients with severe penile deformity.

Table 3 shows the incidence of cryptorchidism and/or hypoplasia of the testis in 97 patients with

hypospadias who had an enlarged utricle and who underwent the hCG stimulation test. The incidence of cryptorchidism for each grade of utricle was: Grade 0, 11% (2/18); Grade I, 18% (10/57); Grade II, 29% (5/17); Grade III, 60% (3/5). The incidence of hypoplasia of the testis for each grade of utricle was: Grade 0, 17% (3/18); Grade I, 21% (12/57); Grade II, 29% (5/17); Grade III, 20% (1/5). The incidence of both cryptorchidism and hypoplasia of the testis increased according to the severity of utricular enlargement.

Basal levels of serum testosterone were similar in controls, in patients with Grades 0 and I utricles, and those with Grades II and III utricles (9.8 ± 0.6 versus 7.1 ± 0.6 versus 8.4 ± 1.4 ng/dl). The highest levels of serum testosterone were found in control subjects after hormonal stimulation and a statistically significant difference was evident between the peak levels of testosterone in controls and in patients with Grades II and III utricles (375 ± 73 versus 229 ± 24 ng/dl; $P < 0.05$) (Fig.). There was also a significant difference in peak levels of testosterone between patients with Grades 0 and I utricles, and those with Grades II and III (314 ± 19 versus 229 ± 24 ng/dl; $P < 0.05$) (Fig.). No statistically significant difference was observed in the maximal levels of testosterone between controls ($n = 5$) and all other patients ($n = 97$) (375 ± 73 versus 295 ± 17 ng/dl).

Table 1 Degree of Hypospadias

	No. of patients (%)
Glanular	88 (16.7)
Penile	204 (38.7)
Penoscrotal	122 (23.1)
Scrotal	101 (19.1)
Perineal	13 (2.4)
Total	528 (100.0)

Table 2 Relation between Penile Deformity and Grade of Prostatic Utricle in Patients with Hypospadias

Degree of hypospadias	No. of patients	Grade of utricle		Total no. of patients (%)
		G0+GI	GII+GIII	
Glanular+ penile	272	70	4	74 (27.2)
Penoscrotal	106	30	9	39 (36.8)
Scrotal+ perineal	107	33	27	60 (56.1)
Total	485	133	40	173 (35.7)

Discussion

It is known that androgenic hormones secreted by fetal testicular tissue are essential to the development of the wolffian ducts, urogenital sinus, and the transformation of the bisexual genital rudiments to the male external genitalia (Jost, 1970; Imperato-McGinley and Peterson, 1976). Testicular hormonal synthesis begins at 8 weeks' gestation, corresponding to the increased levels of chorionic

Table 3 Incidence of Cryptorchidism and Testicular Hypoplasia in Patients with Hypospadias and Enlarged Prostatic Utricles who Underwent the hCG Stimulation Test

Grade of utricle	No. of patients	Cryptorchidism		Hypoplasia of testis	
		Unilateral	Bilateral	Unilateral	Bilateral
G0	18	1	1	1	2
GI	57	9	1	5	7
GII	17	3	2	2	3
GIII	5	0	3	0	1
Total	97	13	7	8	13

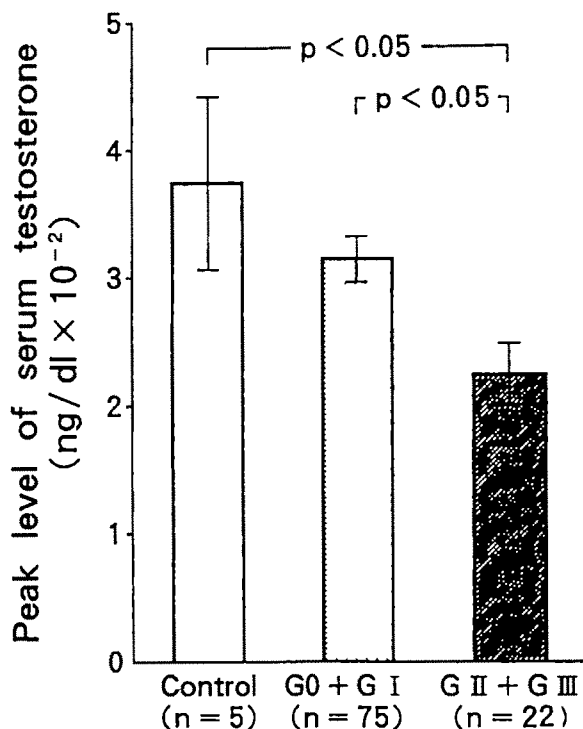


Fig. Peak levels of serum testosterone after 3 days' hCG stimulation in patients with hypospadias and enlarged prostatic utricle. Figures in parentheses are numbers of patients and endocrinologically normal boys. G=grade of utricle. Values of serum testosterone are expressed as mean plus or minus standard error of mean.

gonadotrophin in the male embryo (Reyes *et al.*, 1974). The wolffian duct starts to develop at the same time. Male differentiation of the urogenital sinus and external genitalia is followed 1 week later by stimulation of 5 α -dihydrotestosterone reduced from testosterone by 5 α -reductase in the target tissues (Siiteri and Wilson, 1974).

Although the cranial part of the prostatic utricle is derived from the müllerian duct, and the caudal segment from the urogenital sinus, müllerian and wolffian ducts, it is thought that utricular enlargement may be caused primarily by androgenic insufficiency during the critical period of organogenesis (Devine *et al.*, 1980; Ikoma *et al.*, 1985). It has been confirmed by the present study of a larger number of patients with hypospadias that the higher grade utricles (II and III) are found more often in patients with a severe degree of penile deformity (Howard, 1948; Shima *et al.*, 1979; Ikoma *et al.*, 1985). In addition, the lower levels of serum testosterone following hCG stimulation in

patients with hypospadias associated with the high grade utricles supports the hypothesis that insufficient or delayed androgenic action during the critical period of sexual differentiation in the male embryo is primarily responsible for the utricular enlargement. An increased incidence of both cryptorchidism and hypoplasia of the testis also suggests that utricular enlargement is an androgen-dependent phenomenon.

An important point is whether the patients had a family history of incomplete male pseudohermaphroditism, either type 1 or 2 (Walsh *et al.*, 1974; Wilson *et al.*, 1974). In the present study, patients with perineal hypospadias and Grade III utricle were excluded on the grounds of possible pseudo-vaginal perineoscrotal hypospadias due to 5 α -reductase deficiency (Type 2). The family history was also carefully studied to rule out the Reinfenstein syndrome (Type 1). However, patients with hypospadias who had partial androgen insensitivity without a familial cluster might not have been eliminated completely, since androgen receptor assay of the target tissue was not carried out in every case. A study of androgen receptor levels in patients with enlarged prostatic utricles is now under way and we have already concluded that patients with isolated hypospadias (no associated anomalies) do not have impaired androgen receptor activity (Terakawa *et al.*, 1990).

Another study of isolated hypospadias also suggests that the conversion of testosterone to 5 α -dihydrotestosterone by 5 α -reductase and the binding of 5 α -dihydrotestosterone to the androgen receptors in the genitalia are not impaired in these patients (Gearhart, 1988). Androgen receptor levels in patients with hypospadias and utricular enlargement must be investigated in order to reveal the possible involvement of androgen receptors in the aetiology of enlarged utricles, since part of the utricle is derived from the urogenital sinus, which is the target tissue of 5 α -dihydrotestosterone (Imperato-MacGinley and Peterson, 1976).

The activity of the müllerian inhibiting substance, a fetal regressor of müllerian ducts, does not influence enlargement of the utricle, since female internal organs such as the fallopian tube and uterus should develop under the impaired action of this hormone (Jost, 1970; Josso *et al.*, 1977; Devine *et al.*, 1980).

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Abstracts of the Proceedings of the Urological Society of Australasia, 44th Annual Scientific Meeting, Gold Coast, Australia, 1991

President: E. G. Holmes
Secretary: P. M. McDougall
Editor: R. J. Millard

The 44th Annual General Meeting of the Urological Society of Australasia was held at the Sheraton Mirage Resort, Gold Coast, Queensland from 14 to 19 April 1991. The meeting was organised by Mr Graham Holmes, President of the Society, and a committee of local members. Principal guests of the meeting were Professor David Barrett of the Mayo Clinic, Rochester, USA, Professor Philip Belitsky of Dalhousie University, Halifax, Canada, Professor Frans Debruyne of Nijmegen, The Netherlands, Professor Scott McDougal of Harvard Medical School, Boston, USA, and Professor Tony Mundy of Guy's Hospital, London.

The theme was continuing medical education and the scientific convenor, Mr Geoffrey Hirst, changed the format of the meeting to accommodate the requirements of this theme. The major topics covered were carcinoma of the prostate and urinary incontinence. All podium presentations were educational and given by invitation by local and international experts to cover the entirety of the subject from basic science to latest clinical advances. The principal guests also contributed state-of-the-art keynote presentations. The scientific papers were confined to poster presentations in a series of expanded sessions.

The Harry Harris Oration was delivered by Professor G. J. Bolton, Professor of Modern History, University of Queensland, on the subject, "How to teach old dogs new tricks".

The Keith Kirkland prize for the best paper presented by a trainee was awarded to Dr D. Bolton for his paper on a sutureless Nd:YAG laser vasovasostomy.

The Alban Gee prize for the best poster presentation was won jointly by Dr R. Bevan for her poster on alpha 1 adrenergic receptor subtypes in the urethra and Mr A. Costello for his on laser prostatectomy.

The 45th ASM of the Society will be held at the Hyatt Hotel, Adelaide, South Australia, between 29 March and 2 April 1992.

Carcinoma of Prostate

Subcapsular Orchiectomy using the CO₂ Laser

D. M. Bolton and A. J. Costello

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Subcapsular orchiectomy was described in 1942 and has been widely practised by urologists because of its cosmetic appeal. After reports identified the presence of Leydig-like cells in the tunica albuginea following this procedure,

its popularity waned. Hormonal studies have subsequently identified a testosterone profile identical to that following bilateral orchiectomy.

Carbon dioxide laser subcapsular orchiectomy was first described in 1988 by Johnson and Wishow. They proposed a method to combine the cosmetic advantages of subcapsular orchiectomy with the haemostatic potential of the CO₂ laser, thus potentially reducing the incidence of post-operative haematoma and wound infection.

Eighteen patients have been treated using this technique at our institution. Pre- and post-operative serum testosterone levels were recorded in all patients and beta-

HCG stimulation testing for residual androgen secreting tissue was also performed in 10 cases.

All patients were shown to have castrate levels of testosterone following the procedure and to show a castrate response to beta-HCG stimulation. No post-operative complications occurred and operating time was equivalent to that for conventional subcapsular orchiectomy.

We conclude that CO₂ laser subcapsular orchiectomy is a satisfactory method of hormonal manipulation therapy.

Peri-operative Measurement of Prostate Specific Antigen during Transurethral Prostatectomy

A. P. Seigmund, Z. S. Wisniewski, J. C. Stanley, R. I. Hill, R. McMullin and N. Buxton

Sir Charles Gairdner and Repatriation General Hospital, Perth, Western Australia

The aim of this study was to examine the effects of transurethral resection (TURP) on serum prostate specific antigen (PSA) during and up to 4 days after the operation.

Twenty-one patients (16 with benign prostatic hyperplasia and 5 with prostatic carcinoma) undergoing routine TURP had serial PSA measurement at the start, mid-point and end-point of the resection and daily until discharge from hospital.

With benign hyperplasia the PSA rise was immediate and high but fell within 24 h of surgery. However, with adenocarcinoma the changes appeared to reflect the degree of differentiation of the tissue.

We conclude that PSA should not be measured until the fifth post-operative day following TURP and until the histopathology of the resected tissue is known. PSA measurement may thereafter be useful for further management of patients.

Early Orchiectomy for Carcinoma of Prostate

J. P. O'Collins

Melbourne, Victoria

Since 1975 a total of 551 patients with prostatic cancer have been treated by orchiectomy. Patient selection was based on the finding of more than 10% of prostatic chips from TURP specimens being positive for cancer or patients with a PSA level >50 or a prostatic acid phosphatase >25, or metastatic disease. Patients were followed up 3-monthly for 1 year and 6-monthly thereafter by PSA, PAP and alkaline phosphatase levels. The results were correlated with histological grading of the tumours, amongst which 285 were well differentiated, 135 were moderately and 131 were poorly differentiated.

Overall mortality in 551 patients was 67 from carcinoma and 52 from other causes. Of well differentiated carcinoma patients aged 55 to 70 years, 59 were alive 1 to

13 years later, 5 died from carcinoma and 2 died from unrelated disorders. Well differentiated carcinoma in men over the age of 80 showed that 13 had died of unrelated factors and 54 were alive 1 to 8 years later. In 31 poorly differentiated tumour patients aged 55 to 70, 15 were alive 1 to 14 years later, 15 died from cancer and 1 died of unrelated disease. In patients over 80 with poorly differentiated tumours, 5 died from cancer, 4 died of unrelated factors and 18 were alive and well 1 to 8 years later.

Long-term survival for patients with well and moderately differentiated tumours were similar to life expectancy tables for the state of Victoria. By contrast, those with poorly differentiated tumours had a poorer prognosis. Orchiectomy appears to confer upon those patients with well and moderately differentiated tumours a normal life expectancy.

Nd:YAG Laser Ablation of the Prostate as an Alternative to TURP

A. J. Costello, D. E. Johnson, D. M. Bolton and W. G. Bowsher

St Vincent's Hospital, Melbourne, Victoria

Previous attempts at laser ablation of prostatic adenoma have been unsuccessful owing to inability to aim laser energy directly into the prostatic tissue. Using a beam deflection fibre, an initial cohort of patients with prostatic outflow obstruction has been treated by laser therapy.

Results have indicated improvement in patient symptom score and flow rate following laser therapy. Histological analysis of tissue resected following laser ablation demonstrated marked cellular denaturation following the procedure. These changes were noted throughout the treated area out to the capsule.

These preliminary results are encouraging and the technique deserves further evaluation in order to determine its effectiveness as a therapy for bladder outlet obstruction secondary to benign prostatic hypertrophy.

A1 Carcinoma of Prostate—A Not So Innocent Lesion

D. Gunter

Melbourne, Victoria

In the last 10 years, 51 patients were seen who had 5% or less of well differentiated carcinoma of prostate in TURP specimens. They were classified as having Tis, NO, MO disease. Fifteen of these (30%) had a history of acute or chronic prostatitis. Second-stage TURP biopsies were performed on 35 patients. Of these, 13 patients had positive biopsies and 11 of them received primary treatment. Radical prostatectomy was performed in 6, all of whom have no evidence of disease. Five received radiotherapy and 2 of these have proven local recurrent disease. Two frail, elderly, biopsy-positive men had no

primary treatment and 1 of these died of carcinoma at 36 months.

Later development of active carcinoma of prostate (CaP) occurred in 7 of 22 biopsy-negative patients

Sixteen patients did not undergo second-stage biopsy. Two of these have proven local recurrence, 1 had more CaP at radical prostatectomy and 3 have died of unrelated disease.

Overall, 47% of patients (24/51) have been found to have further carcinoma at a second look or have subsequently been found to have a carcinomatous recurrence. If untreated, local progression or metastatic spread occurred in 28% (10/36).

It is recommended that patients presenting with A1 (Tis) carcinoma of the prostate be carefully checked by second-stage TUR biopsy for residual disease. An active treatment programme seems justifiable in those who are biopsy-positive. Careful follow-up is required for all patients, for this is clearly not a benign disease.

Chemotherapy of Advanced Prostate Cancer

R. Muschter

Munich University, Munich, Germany

In spite of many attempts to treat advanced cancer of the prostate, more than 50% of patients with metastases show progression within 1.5 to 3 years. The mean survival of these patients is less than 1 year. The fate of primary or secondary hormone resistance of these tumours has led to numerous drug trials and many studies of cytotoxic agents have been reported

Attempts with different agents as monotherapy or in combination showed the need for a controlled randomised study to compare any beneficial effects, including complete and partial remission, increased interval to progression, longer survival or better quality of life. The objective response to chemotherapy with cytotoxic agents of advanced hormone-resistant prostate cancer is poor, with less than 40% stable disease or remissions even in the most optimistic studies. Polytherapy appears no better than monotherapy. The most effective agents appear to be epidoxorubicin and mitomycin.

The possible benefits of using interferons in prostate cancer therapy include antiproliferative effects on tumour cells, such as changes in membrane antigens and receptors, inhibition of cell growth and reversion of malignancy, as well as immunomodulative effects such as activation of macrophages and lymphocytes and the expression of antigens.

In all, 57 patients have been studied but the results are inconclusive, with response rates ranging between 0 and 79%. The promising results of interferon therapy seen in other malignancies has not been evident in prostate cancer.

Prostatic Cancer in Men under the Age of Fifty

R. M. Snow

Alfred Hospital, Melbourne, Victoria

Seven men with cancer of the prostate presented at ages ranging from 43 to 49 years. All presented with obstructive urinary symptoms. Four patients with localised disease tended to have less severe symptoms than those with advanced disease, where the obstruction was severe or associated with irritative symptoms. Five patients had a clinically suspicious gland proven to be malignant on aspiration cytology.

Two patients with Stage A1 disease are doing well, with no local progression and no demonstrable disease despite not having had definitive therapy. They are under close surveillance follow-up. A further 2 patients with Stage B disease appear disease-free after radical prostatectomy, with follow-up of 28 and 32 months respectively. In general, the patients with localised disease had well differentiated tumours.

Of 3 patients with extracapsular, poorly differentiated disease, 1 is dead (at 42 months) and 1 has progressive disease. The third has only recently completed X-ray therapy. The age at presentation of these 3 patients was 43, 44 and 46 years.

In this small group of patients, those with low stage, better differentiated tumours have done well. Higher stage, poorly differentiated tumour appears unresponsive to treatment and the patients are not doing well. Prognosis appears to be determined by stage and grade of tumour rather than the age of the patient.

A Local Anaesthetic Technique for Tru-cut Transrectal Prostatic Biopsy

R. F. Smart

Palmerston North, New Zealand

Tru-cut transrectal prostatic biopsy is traditionally done under general anaesthesia on an in-patient. Multiple needle passes may be required to obtain representative tissue and the procedure carries a risk of bacteraemia. Out-patient fine needle aspiration cytology was therefore developed. The material obtained can be difficult to interpret histologically or cytologically compared with that obtained from a Tru-cut needle. A local anaesthetic technique was therefore developed for use with transrectal Tru-cut biopsy

Twenty ml of 1% lignocaine solution are instilled into the anal canal, using the applicator used for urethral instillation. The patient sits upright for a few minutes to keep the solution as low as possible in the anal canal and rectum. Using the same technique, 1 g ceftriaxone is instilled into the rectum and 160 mg gentamicin are given intravenously before biopsy. A further injection of 80 mg

gentamicin is given 8 h later. All patients were discharged on oral tetracycline for 4 days.

A total of 61 patients have had transrectal Tru-cut biopsies by this technique. An effort was made to use only a single pass of the needle during biopsy. All patients found the procedure acceptable and adequate biopsies were consistently obtained. Only 1 mild episode of clinical bacteraemia was seen.

Transrectal Tru-cut biopsy of the prostate under local anaesthesia would appear to be an achievable and safe procedure.

Management of Spinal Cord Compression in Patients with Metastatic Carcinoma of the Prostate H. Mameghan, C. Milross, R. Fisher, M. Davis, W. Stening and J. Mameghan

Prince of Wales and Prince Henry Hospitals, Sydney, New South Wales

We have reviewed the records of 32 patients treated for spinal cord compression from metastatic carcinoma of the prostate treated at our hospitals between 1980 and 1989. The aim of the study was to identify prognostic factors and types of treatment associated with a favourable outcome. Outcome was determined by comparing neurological status (from the occurrence of 5 symptoms and 4 signs) both at presentation and again at 1 month. The symptoms analysed were pain, sensory disturbance, subjective weakness, bladder discomfort and bowel discomfort; the signs were sensory loss, motor loss, loss of ambulation or the need for a urinary catheter. Outcome variables were analysed separately and in combination in an overall measure of outcome called a functional improvement score (FIS). The FIS was defined *a priori* as a weighted sum of the changes in status of pain, weakness, ambulation and catheter status.

There was a net improvement in 7 of 9 symptoms and signs, the exceptions being bladder and bowel symptoms. In particular, 28 patients had pain at presentation compared with 18 at 1 month (a 31% improvement). Overall improvement as measured by an increase in FIS occurred in 72% of patients.

Prognostic factors studied were age, year of presentation, performance status and delay in treatment, and none of these was predictive of outcome.

Patients treated by surgery and post-operative radiotherapy fared better than those treated by radiotherapy alone or surgery alone, but the differences did not reach statistical significance ($P=0.14$).

It was concluded that the majority of patients did benefit from treatment in this emergency situation, that there were no clearly identifiable factors predicting improvement and that there may be some advantage in using combined surgery and radiotherapy.

Keith Kirkland Prize Papers

Active Surveillance for State 1 Non-seminomatous Germ Cell Tumours—Safe despite Adverse Factors

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Two-thirds of all patients with stage 1 non-seminomatous germ cell tumours of the testis (NSGCT) will be spared further therapy when treated by orchiectomy and active surveillance alone. This approach has been criticised as being inappropriate in patients who have multiple "risk factors", among whom as many as 60 to 70% may relapse.

Long-term follow-up was studied in 45 patients with clinical Stage 1 treated by active surveillance over the last 10 years. Follow-up averaged 4.1 years (range 20 months–8 years) and during this time 13 patients relapsed, 11 of them within 18 months. Post-chemotherapy follow-up was available to an average of 4.3 years. All relapsed patients were salvaged with standard first-line chemotherapy; 2 had retroperitoneal lymph node dissection for residual benign masses. Morbidity from long-term chemotherapy was low.

High T stage of original tumour, embryonal histology, vascular invasion and scrotal violation were again shown to convey an increased rate of relapse. The low morbidity and reliability of sustained follow-up in this series indicated that surveillance may be offered to all patients with Stage 1 disease despite the presence of adverse risk factors.

The Effect of Digital Rectal Examination on Prostate Specific Antigen Levels

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In order to assess whether digital rectal examination had an effect upon serum prostate specific antigen (PSA) levels, serum samples were taken from 54 patients before, 30 and 120 min and 18 h after a single rectal examination of the prostate. Four categories of patients were examined—those with initially normal or initially elevated PSA levels, subdivided into those with benign or malignant disease.

In all but one subgroup there was no significant difference in the before and after PSA levels. The group with initially normal PSA and benign prostates showed a statistically significant elevation of PSA at the 30-min interval alone. However, the mean difference in PSA levels was 0.06 ng/ml. This is below the technical sensitivity of the assay (0.1 ng/ml) and is well below the known random daily variation of 10 to 20% in PSA levels.

The largest individual variation was 0.3 ng/ml but despite this no patient changed from normal to elevated PSA levels.

It was concluded that digital rectal examination of the prostate had no clinical effect upon serum PSA levels.

Development of a Sutureless Nd:YAG Laser Vasovasostomy over a Biodegradable Intraluminal Stent

D. Bolton, A. J. Costello, P. Eadie and Y. Ikada
St Vincent's Hospital, Melbourne, Victoria, and Kyoto, Japan

The large number of vasectomies performed annually in western countries makes vasectomy reversal a commonly requested procedure. Standard microsurgical techniques for vasal reanastomosis require training in microsurgery and lengthy operating times. Success for pregnancy is only 50% in the best series and failure to maintain patency due to anastomotic fibrosis accounts partially for this.

We have attempted to develop a totally sutureless method of vasovasostomy over a lactic acid biodegradable stent. Precise tissue approximation has been achieved using the New Zealand white rabbit as a model. The procedure has been performed at a power setting of 2 watts using an Nd:YAG laser with a hand-held 600 micron quartz fibre in a non-contact rotational delivery technique.

The results were assessed using semen analysis and by histological examination of the ultrastructure of the weld. Surgeons untrained in microvascular surgery readily adapted to the laser vasovasostomy technique.

Laser vasovasostomy appears to offer a simpler, faster and possibly more effective technique of vasal reanastomosis and the techniques developed may have widespread applications in surgery.

Does Detrusor Contractility Affect the Outcome of Transurethral Resection of the Prostate?

S. D. Mark, R. von Mastrigt and E. P. Arnold
Christchurch, New Zealand

The outcome of transurethral resection of the prostate (TURP) is occasionally poor. In some cases this is found to be due to reduced bladder contractility. A prospective study was carried out on 25 patients undergoing routine TURP to see if the outcome was affected by the pre-operative detrusor contractility; we then attempted to identify pre-operative factors that might indicate patients with poor contractility.

The outcome was measured 6 months post-operatively and revealed improved symptom scores and improved urinary flow rate. Contractility (force and velocity) was

measured using an *in vitro* assessment of detrusor muscle strips obtained endoscopically at the time of TURP.

Post-operatively there was a significant improvement in both symptom scores and flow rates. The improved symptom scores correlated with the improved flow rates.

Pre-operative contractility assessment was predictive of a good subjective response to TURP at 6 months. Similarly, there was a trend for contractility to correlate with improved post-operative flow rates, this did not reach statistical significance, possibly because of the small numbers concerned.

Pre-operative subjective and objective criteria did not correlate with contractility measurements. Therefore we were unable pre-operatively to identify patients with reduced contractility who were likely to do poorly following prostatectomy.

Urinary Mutagenicity and Uro-enteric Tumour Formation

R. B. Thomas, R. S. U. Baker, S. Greenwell and M. Kennedy

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The use of bowel in the urinary tract is associated with a risk of developing neoplasia. In ureterosigmoidostomy the incidence of adenocarcinoma in the colonic segment has been estimated as being 500 to 700 times greater than that found in an age-matched population. These tumours have been linked to the presence of urinary nitrosamines. Colonic tumour induction has been demonstrated in a rat model of vesicosigmoidostomy.

Because the causal role of nitrosamines is speculative and their identification is costly, we have attempted to detect carcinogens indirectly by measuring their mutagenic effects with the Ames bacterial mutation assay, which measures the mutation of histidine-dependent bacteria to histidine independence.

Twenty animals underwent vesicosigmoidostomy and 10 of them survived to the end-point of 33 weeks; 10 animals were non-operative controls. A 24-h urine collection was obtained from each animal 4 times and subjected to the mutagenesis assay. The colon from the mid-transverse colon to anus was examined histologically.

Of 9 operative specimens suitable for analysis, 4 showed colonic dysplasia at the anastomotic site. No lesions were found in the control group. The bacterial revertant frequencies of the urine of those animals displaying histological changes at the anastomosis did not differ significantly from either the other operative animals or from the controls. The demonstration of neoplastic changes in the face of negative mutagenicity results throws doubt on the significance of urine-borne carcinogens such as nitrosamines being major factors in the development of neoplasia, and suggests that the influence of other factors acting at the anastomosis may be of importance in causing neoplasia.

Reconstructive Surgery

Clinical Experience with the Invaginated Sleeve Technique for Continent Cystostomy—Preliminary Report

R. A. Gardiner

University of Queensland, Brisbane, Queensland

An invaginated sleeve cystostomy has been used for 5 patients requiring a continent cystostomy. All had had difficulty in managing clean intermittent self-catheterisation (CISC).

In 4 of the 5 patients the cystostomies were continent post-operatively. The one failure had the intramural part of the graft disrupted by passage of a feeding tube on days 5 and 8 because of leakage though an exposed fenestration.

Patients have practised CISC through the cystostomy for 37, 26, 7 and 1.5 months. The first 2 patients are dry, apart from occasional slight leakage from both the cystostomy and urethra when the bladder is very full. The third patient was totally continent but stopped catheterising because she developed a "body image" problem. The fourth patient continued to leak from the urethra and opted for a permanent suprapubic catheter.

Only one patient required a review of the stoma. A V-Y plasty was performed at 3 months for a discrete stenosis at the mucocutaneous junction. There has been no recurrence of the stenosis during 26 months of follow-up. In this case the bladder had not been hitched to the back of the anterior abdominal wall. Traction ischaemia is thought to have been responsible for the stenosis.

The invaginated sleeve technique is a simple procedure for providing a continent cystostomy. Bladder capacity is maintained and non-urinary tract structures are not required.

Clam Cystoplasty

S. D. Mark, E. P. Arnold, C. U. McRae and S. P. Gowland

Christchurch, New Zealand

The aim of clam cystoplasty is to create a low pressure bladder. Recent results have been poorer than those originally claimed. We reviewed our 25 patients in an attempt to understand our failures.

Of the original 25 patients, 12 were dry and considered their operation a success; 13 were still wet and 5 of these (20%) had persistent high pressure instability with urge incontinence. No pre-operative factors could be identified that would have identified these patients pre-operatively. Five patients had stress incontinence with low pressure bladders; all 5 had a pre-operative history of stress

incontinence and had incompetent open bladder necks on videourodynamic studies remote from unstable detrusor contractions.

Three patients amongst our failures were males with neurogenic bladders. Two patients had overflow incontinence and were elderly. They were unable to manage intermittent self-catheterisation. One has a permanent indwelling catheter and the other is wet.

Our results could have been improved by combining an anti-stress operation with clam cystoplasty in those patients who had a pre-operative history of stress incontinence and an open bladder neck on testing. In addition, in the elderly we now perform clam cystoplasty only as a last resort in those who can manage intermittent catheterisation.

Ileal Conduits—A Warning

A. Woodward

Royal Children's Hospital, Melbourne, Victoria

Between 1955 and 1975, over 400 ileal conduit diversions were performed on patients with spina bifida at this hospital at an average rate of 20 per year. Some 15 to 25 years later these patients are developing problems—chronic inflammatory changes and stricture formation in the conduit and distal ureters causing hydronephrosis and renal parenchymal damage. Major revisions of strictured conduits with either ileal conduit replacement or undiversion surgery have been performed at a rate of 10 to 12 per year throughout the period 1985 to 1990.

Many of our patients have been lost to follow-up. In order to contact these and similar patients with a view to encouraging them to seek urological follow-up, a pamphlet detailing the long-term problems that may arise in patients with ileal conduit diversions will be distributed throughout Australia by stoma equipment suppliers.

Augmentation Cystoplasty in Children

A. Woodward

Royal Children's Hospital, Melbourne, Victoria

The early results of 30 augmentation cystoplasties performed on spina bifida children have been analysed. Most procedures (23) were performed for intractable incontinence but 5 were undiversion procedures and 2 were carried out for renal deterioration.

The technique used was to take 25 cm of detubularised ileum and use it as a cup cystoplasty in 23 patients and as a clam cystoplasty in 7. An artificial sphincter was implanted synchronously in 9 patients and a further 5 had an auxiliary colposuspension procedure.

Pre-operative urodynamic assessment showed poor bladder compliance with leak point pressures in excess of 40 cm of water. Post-operatively there was increased compliance with pressures of 15 to 30 cm of water at a

capacity of 300 ml. Satisfactory continence with clean intermittent catheterisation was achieved in all cases, although it is worth remembering that 14/30 had required augmentation of their outlet resistance.

Significant complications included 2 patients in whom the cystoplasty ruptured, requiring surgical repair. Two children developed bladder calculi and 4 had recurrent cystitis. One patient developed adhesion obstruction and 1 child died from V-P shunt obstruction unrelated to the urological procedure.

The short-term results of augmentation cystoplasty appear to be satisfactory. It is too early to predict what the long-term sequelae might be in this group of children, especially in those who already have compromised upper tracts at the time of augmentation.

The One-stage Bilaterally Pedicled Island Skin (BIPIPS) Procedure for Bulbar Urethroplasty

J. Wong, C. R. Chapple and R. T. Turner-Warwick
London, UK

A short bulbar stricture that can be excised and reanastomosed offers the potential of a 100% stricture-free result. However, for long bulbar strictures in which urethrotomy does not offer a permanent cure substitution urethroplasty may be required.

Pedicled flaps offer good vascularisation and reduce the incidence of graft failure when compared with free grafts. Penile skin has the advantages of being "moisture resistant" and virtually hairless. Compared with scrotal skin it has a lower incidence of stone formation, encrustation and eczematous changes when used for substitution urethroplasty in long bulbar strictures.

A total of 73 patients who had undergone the BIPIPS/augmented roof strip procedure were followed up 1 to 6 years later. A restenosis rate of 6% was found. In those requiring further surgery a subsequent repair was effected by simple anastomotic redeployment.

Pathology and Results of Treatment in Pelvic Fracture Urethral Distraction Defect Injuries—Review of 621 Patients

J. Wong and R. T. Turner-Warwick
London, UK

A review has been conducted of 621 cases of pelvic fracture urethral distraction defect repairs performed between 1974 and 1989. A variety of repair procedures performed during this period fell into 2 broad categories.

In patients with a normal bulbous urethra, who had had no previous surgical intervention, it was invariably possible to repair the urethra by a direct anastomotic technique. This was achieved either from a perineal approach or by a synchronous perineal and suprapubic

approach, sometimes necessitating transpubic access. In such patients the restenosis rate was approximately 1%. However, in similar cases where a previous repair had been attempted and where the bulbar urethra was abnormal, the restenosis rate in the long-term follow-up approached 4%.

Patients with longer defects required regeneration and/or substitution urethroplasties rather than direct anastomotic repair. The restenosis rate of these repairs when followed up for 3 years or more was 14%.

The long-term success rate of urethral reconstruction after pelvic fracture urethral injury depends upon the state of the bulbous urethra. Previous failed surgical repair jeopardises the chance of a favourable outcome.

Calculus Disease

Residual Stones following Extracorporeal Shock Wave Lithotripsy—The Case for Citrate Prophylaxis

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Flinders Medical Centre, Adelaide, South Australia

Retention of fragments within the kidney after extracorporeal shock wave lithotripsy (ESWL) continues to be a major shortcoming of this form of stone treatment. The aim of this study was to evaluate the ability of sodium-postassium citrate to inhibit calcium oxalate crystal nucleation and growth on to stone fragments remaining after ESWL.

The continuous flow crystallisation technique was adapted to induce calcium oxalate crystal nucleation and growth on to the surface of fragmented kidney stones and the inhibitory effect of sodium-postassium citrate was assessed by scanning electron microscopy and by determining the relative increase in crystalline mass at final concentrations of 0, 2, 4, 6, 8 and 10 mmol/l.

Sodium-postassium citrate significantly inhibited the deposition of new crystalline calcium oxalate in a dose-dependent manner above 2 mmol/l; these findings were confirmed by scanning electron microscopy.

It was concluded that sodium-potassium citrate may provide an effective means of preventing the formation of new stones by the deposition of calcium oxalate on to residual stone fragments resulting from ESWL. The technique used is an efficient means of testing the efficacy of therapeutic agents to prevent stone recurrences in patients treated with ESWL.

Local Experience with the Candela Laser Lithotripter

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Since the initial description of its use in clinical practice in 1987, lithotripsy using the Candela pulsed dye laser has become an accepted technique in the management of ureteric calculi. Between June and December 1990 an initial cohort of 23 patients was treated at this institution using the Candela MDL-1 laser lithotripter.

The majority of patients were discharged from hospital stone-free after only 1 treatment. Post-operative morbidity and bed stay were comparable to conventional ureteroscopy but not statistically significant owing to the small numbers involved.

In one subgroup of patients with low stones the previously unreported use of caudal anaesthesia alone was attempted. This appeared to give perfectly adequate anaesthesia for the treatment of ureteric stone by laser lithotripsy provided that the stone was low in the ureter and that ureteric dilatation was not required in order to gain access. The combination of these techniques might make the treatment of ureteric stones a day-case procedure.

Urolithiasis—A Sex-linked Disease?

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The inclusion of urinary proteins within calcium oxalate crystals is highly selective, with one protein, crystal matrix protein (CMP), being predominantly absorbed. Elsewhere we have shown that CMP is a potent inhibitor of calcium oxalate crystallisation in urine and that its content in crystals derived from female urine exceeds that in crystals from men. Since these findings may have implications in the aetiology of stone disease, the aim of the study was to determine whether the concentration of CMP in the urine of normal women is greater than that in normal men or whether female CMP binds more avidly to calcium oxalate crystals.

The CMP concentration was measured in 24-h urine samples from 20 men and 20 women, using an ELISA assay. The median concentration was not significantly different ($P < 0.05$, $n = 20$). Ultrafiltered urine was therefore dosed with CMP derived from either male or female urine. Crystallisation was induced and the CMP content of the precipitated crystals measured. At all concentrations tested the amount of female CMP isolated from the crystals was approximately double that of the male counterpart, indicating a stronger binding affinity of the protein for the crystals.

This difference implies that male and female CMP are molecularly distinct, the origin of which must be sex-linked. This may explain the lower incidence of urolithiasis in women.

Plasma Renin Activity Changes in Extracorporeal Shock Wave Lithotripsy (ESWL)—The Question of Hypertension

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Munich University, Munich, Germany

ESWL creates a certain degree of renal trauma and the question of whether it is associated with the development of hypertension is still the subject of debate. Chronic elevation of renin activity after ESWL could be a cause of the hypertension sometimes observed. The aim of the study was to examine the excretion of renin during and after ESWL therapy.

Thirteen pigs weighing approximately 35 kg were given renal vein catheters on both sides. Before, during and after ESWL treatment of one kidney with 3000 shock waves in a Dornier HM3 lithotripter working at a generator voltage of 18 kV, blood samples were taken from both renal veins. The renin activity was measured by the amount of angiotensin I per ml per hour.

There was no change in the renin activity of the non-treated kidneys and the controls. Renal vein blood from the treated kidneys showed a high peak within 500 to 1000 shock waves, decreasing to normal levels during ongoing treatment. Another much smaller peak was seen within 5 to 15 min after treatment and this returned to normal levels within 30 min.

The short-lived increase in renin activity during ESWL treatment may be due to mechanical effects of the shock waves on the kidney or to necrosis of renin-producing cells. Although the origin of the increase remains unknown, it is temporary. There is no evidence of prolonged or permanent changes in plasma renin activity in association with ESWL treatment.

Incontinence

Rectus Sheath Fascial Sling: Preliminary Report

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The rectus sheath fascial sling is fashioned from 2 longitudinal strips from the abdominal wall either side of the linea alba. These strips are tunnelled retropubically to be sutured to the bladder neck and proximal urethra in an overlapping fashion, providing sling support. The procedure is performed on poor risk patients, including those with gross obesity, previously unsuccessful surgery and coexistent detrusor instability. We report our experience with 13 patients who have been followed up for 12 to 29 months.

The first 9 patients had stable bladders with gross

stress incontinence, vault descent and urethral incompetence. Four patients had detrusor instability (DI). All but 2 patients complained of both urge and stress incontinence.

All patients were symptomatically improved. Seven stated that they were totally dry but 1 had demonstrable stress incontinence on videocystometry. Two patients continued to be incontinent and both have DI and have been offered a clam cystoplasty. Another 3 patients have low pressure DI and 2 of these were stable pre-operatively. One of the 4 patients with DI pre-operatively has a stable bladder post-operatively. Two patients state that they are still wet on occasions but this cannot be shown urodynamically.

In all cases the bladder neck and proximal urethra were repositioned successfully to the "intra-abdominal zone". No patient was urodynamically obstructed, although 1 woman who had an ileocystoplasty for interstitial cystitis required self-catheterisation.

Despite routine peri-operative antibiotics, cellulitis occurred in 6 patients, with 3 developing abscess cavities that required packing. Wound discomfort was present for several months in 2 patients, being disabling for one.

The preliminary results have encouraged us to embark upon a larger study involving long-term follow-up with urodynamic and clinical evaluation.

Management of Recurrent Stress Incontinence using a modified Stamey Suspension Procedure

J. S. Taylor

Newcastle, New South Wales

Twenty-eight patients presenting with recurrent stress incontinence were treated by a modified Stamey vaginal suspension procedure using Goretex buttresses 1 cm long adjacent to the bladder neck and also over the rectus sheath. These patients had undergone 41 previous operations, including 21 vaginal repairs, 17 Marshall-Marchetti-Krantz procedures, 2 Burch colposuspensions and 1 Raz procedure. Follow-up ranged from 6 months to 5 years.

A total of 25 patients were cured of their stress incontinence. Three procedures failed, this failure being apparent within 6 months of surgery. No late failures were encountered. The complication rate was high, however, with some type of complication noted in 17 patients. Most complications were minor but suprapubic pain requiring the removal of the slings and buttresses occurred in 3 patients. In 1 patient the Goretex buttress eroded into the bladder and required removal.

This procedure appears to be an effective treatment for stress incontinence with no late failure rate in a small series of patients followed for up to 5 years. The post-operative complication rate was high but most of the problems were treated simply. It is the author's experience that patients with detrusor instability and those with fixed bladder necks have a lower success rate.

Surgical Management of the Neurogenic Bladder in Multiple Sclerosis

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The management of the neurogenic bladder in patients with advanced multiple sclerosis creates many nursing difficulties. If female, the patient may be bedridden or confined to a wheel chair, frequently with flexion contractures and adduction deformities of the hips and invariably incontinent of urine. It is the latter which is often of prime concern to both patients and their carers. A number of treatment options are available but none is without advantages and disadvantages. The 3 most common options are:

1. Permanent indwelling urethral catheter. The use of an 18 F catheter with a 5-ml balloon is preferable. Uninhibited detrusor contractions can be treated by drug therapy as required. The development of a patulous urethra—often secondary to poor catheter management—is an indication for a suprapubic catheter with urethral closure if necessary. Alternatively, a conduit diversion may be considered.
2. Suprapubic catheterisation. This is the treatment of choice, especially in cases where, owing to flexion contractures or adduction deformities, an abdominal stoma is preferable to a urethral catheter. It is also useful after the development of a patulous urethra. Again an 18 F catheter (Malecot or 5-ml balloon Foley) gives ideal drainage and minimal complications.
3. Conduit diversion. This should be reserved for those few patients who have intractable problems with catheter drainage or infection. In these cases it has usually been found that other methods, such as vesicostomy with or without urethral obliteration and anterior transposition of the urethra, are unsatisfactory because of poor drainage, stomal stones, infection and poor patient acceptance.

Polytef Paste in the Treatment of Stress Incontinence in 28 Women

R. F. Smart

Palmerston North, New Zealand

Of 92 women presenting for surgical treatment of stress incontinence, 28 were treated by Polytef paste (Mentor) injection. All patients were over 45 years of age because of the theoretical dangers associated with microembolisation. Fifteen patients had severe stress incontinence, using 4 or more pads per day, and 13 had undergone previous gynaecological surgery for stress incontinence, including 8 patients who had had 3 or more operations.

The first 3 patients were injected using the periurethral technique. The remaining 25 were injected using a cystoscopic technique, with volumes of 3 to 7 ml being

placed at the bladder neck. A Bonano suprapubic catheter was left in place overnight.

Twelve patients (43%) were cured long-term and a further 5 improved to the point that further treatment was not required. However, 11 patients (39%) were unchanged and 7 of these have undergone either a colposuspension or a Stamey procedure successfully. One patient developed a granulomatous pelvic cyst arising from the injection site. This was removed surgically.

Success rates were higher in patients who had had previous vaginal surgery (11/13), compared with 6 of 15 patients who had had no previous surgery. This should be taken into consideration when selecting patients for this type of procedure, together with age and desire to avoid more surgery. Otherwise, conventional surgery would appear to offer more consistent results.

Transvaginal Bladder Neck Suspension for Stress Incontinence

P. L. Royce

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Evaluation of 28 women, mean age 57 years (range 39–80), after a transvaginal bladder neck suspension (TVBNS–Raz) for stress incontinence was undertaken after a mean follow-up of 24 months (range 3–48).

Cure or significant improvement, defined by no stress incontinence and less than 2 pads/day, was seen in 21/28 patients (75%). Seven were not improved and required more than 2 pads/day. Urge incontinence was reduced after TVBNS from 12/28 to 6/28.

The mean hospital stay was 10.8 days (range 7–16) and 2 patients required intermittent self-catheterisation for 10 and 43 days respectively. Operative morbidity was low, with 1 wound infection, 1 vaginal haematoma and 1 patient with a suture in the bladder.

Amongst the 7 patients who failed to respond, 6 had had prior incontinence surgery, 2 weighed over 80 kg, 1 had periurethral fibrosis from a previous pelvic fracture and all had recurrent bladder neck prolapse.

The Raz bladder neck suspension is effective in the treatment of stress incontinence and has a low morbidity rate. Patients with identifiable risk factors for failure should be considered for alternative therapy such as a sling procedure.

An Educational Package on Incontinence for General Practitioners

G. Szonyi and R. J. Millard

Prince Henry Hospital, Sydney, New South Wales

We have reported previously on the level of knowledge of general practitioners regarding the management of incontinence in the community. These studies have demonstrated the need for more education in this field.

As part of a nationwide project to improve the level of treatment of incontinence it was decided to develop an educational package on the subject aimed specifically at general practitioners.

Three open seminars were arranged and general practitioners were invited to discuss their educational needs and their preferences for the format of educational material. From these discussions emerged the critical information on which the content and design of the pack were based.

A simple point-by-point format flip chart of information was developed and tested on a number of incontinence experts to ensure completeness of the information and comprehensibility of the presentation. A slide rule for use in the desk drawer of the consulting room was designed for easy access to commonly required information. The pack included a pad of time and volume charts and a sample chart from which to indicate to patients how the micturition chart should be filled in. A total of 2250 packs were distributed to general practitioners throughout New South Wales through sponsorship from the NSW Health Department.

Preliminary studies on a small cohort of practitioners indicated that their scores on a test of knowledge about incontinence improved following study of the package. A larger formal study is now under way to evaluate the educational value of the pack more thoroughly.

Miscellaneous

Low Irrigant Pressure for Endoscopic Urology

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Absorption of fluid into the circulation during endoscopic procedures is not without hazard, especially in the elderly. The irrigating pressure and the duration of the procedure influence the amount of fluid absorbed. A method was devised to keep the irrigant pressure below 30 cm of water.

A drip stand was clamped to the operating table to ensure that the head of pressure did not change as the table was raised or lowered. A 2-litre bag of irrigant was suspended from the stand by rubber bands chosen to ensure that as the bag emptied the bag rose. Thus the fluid level remained at a constant height of 30 cm above the patient.

Pressure monitoring during bladder filling demonstrated that the intravesical pressure remained low for a long period before gradually rising to 30 cm of water, at which point flow ceased. The scrub sister was asked to observe the drip chamber, which was set at an angle of 45°, and to report any diminution in the drip chain,

whereupon the bladder was emptied immediately. By this method intravesical pressures were kept consistently low and fluid absorption was minimised.

Control pressure studies using standard fixed point irrigant bag suspension demonstrated intravesical pressures up to 60 cm of water at the end point of filling.

Using constant low pressure it is possible to perform transurethral resection of prostate, bladder tumours, ureteroscopy and percutaneous surgery safely and without the hazards of high fluid absorption. This allows for more extensive or prolonged procedures to be performed if necessary.

Comparison of the Responses to Intracavernosal Injection of Various Agents in the Management of Impotence

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The response to the intracavernosal injection of a combination of papaverine and phentolamine, prostaglandin PGE', and a combination of papaverine, phentolamine and prostaglandin PGE', was compared in a randomised crossover manner in 228 men with chronic impotence. The mean age of the group was 61.4 years and comprised 86 men (38%) with arteriogenic impotence, 41 (18%) with venogenic impotence, 56 (25%) with mixed vasculogenic impotence and 45 (19%) with psychogenic impotence. Erectile responses were assessed with real time RigiScan monitoring.

No difference was found in the responses to the combination of papaverine, phentolamine and prostaglandin in any of the aetiological groups but the erectile response to this combination was superior to the other 2 agents in all of the groups, reaching statistical significance in arteriogenic and mild venogenic impotence.

The incidence of prolonged erections was significantly higher with the combination of papaverine and phentolamine than with the other agents. No difference was found between prostaglandin alone and the triple combination therapy group.

Triple therapy with papaverine, phentolamine and prostaglandin PGE' appears to be a safe combination in the treatment of impotence, with a possible role in salvaging patients from treatment failure with other agents.

Ketamine for the Investigation of Lower Urinary Tract Function

R. K. Bevan, M. Rose, K. Duggan, G. F. Murnaghan, S. Copeland, A. R. Mundy and G. Graham
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Ketamine is the anaesthetic agent of choice for the experimental investigation of the lower urinary tract in

many species. We have previously reported considerable variability in pressure responses of the bladder and urethra to filling in the pigtail monkey under ketamine anaesthesia.

The present study examines the rule of ketamine in this variability. Using intravenous infusion to achieve steady state levels, we have shown a significant dose-dependent fall in resting urethral pressure and maximum urethral pressure with increasing doses of ketamine. Ketamine did not significantly affect the bladder parameters measured.

We have also employed *in vitro* radioligand binding techniques, using the alpha 1 adrenergic radiolabel, ³H-methoxyprazosin, to demonstrate that ketamine acts as a competing ligand at the receptor site with a K_d of $7.73 \pm 1.47 \times 10^{-5}$ M and $8.96 \pm 1.88 \times 10^{-3}$ M in the distal and proximal urethra respectively.

Therefore ketamine acts peripherally at the alpha 1 receptor to reduce urethral pressure and by this mechanism may be confounding the normal responses to filling in experimental animals.

Alpha 1 Adrenergic Receptor Subtypes in the Urethra

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Radioligand binding studies were conducted using ³H-methoxyprazosin to label alpha 1 adrenoceptor sites in the sheep bladder and urethra. No receptors were found in the body or base of the bladder in either sex. The label bound with high affinity to single sites in the male and female proximal urethra (K_d = $2.4 \pm 0.8 \times 10^{-11}$ M and $5.48 \pm 2.96 \times 10^{-11}$ M, B_{max} = 2.41 ± 0.34 fmol/mg protein and 0.42 ± 0.12 fmol/mg protein, respectively), and the female distal urethra (K_d = $1.88 \pm 0.86 \times 10^{-10}$ M, B_{max} = 1.53 ± 0.63 fmol/mg protein). It bound with low affinity to a single site in the male distal urethra (K_d = $2.16 \pm 0.73 \times 10^{-9}$ M, B_{max} = 0.85 ± 0.1 fmol/mg protein). These K_d values correspond with published values for alpha 1a and alpha 1b receptor subtypes found recently in the brain and liver tissue from rat and rabbit. Competing ligands, phentolamine, clonidine and noradrenaline did not distinguish between subtypes. This is the first report of alpha 1 adrenoceptor subtypes in the urethra.

Percutaneous and Endoscopic Pyeloplasty

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A series of 29 patients, 18 female and 11 male, were treated for pelviureteric obstruction at a mean age of 49.6

years (range 16–18). Previous surgery had taken place in 16 patients, 9 having had open pyeloplasty and 8 open pyelolithotomy. In 20 patients a percutaneous pyeloplasty was performed and in 9 cases endoscopic balloon dilatation was performed. Double pigtail stents were left in 28 and 1 had a nephrostomy.

For balloon dilatation an Angiocath balloon 1 cm in diameter and 4 cm long was inflated to between 50 and 115 p.s.i. across the pelviureteric junction (PUJ) under X-ray control. A double pigtail stent was left *in situ* for 1 to 3 months.

The percutaneous procedure involved ureterotomy across the PUJ under vision followed by balloon dilatation with a 1×10 cm balloon inflated to 50–110 p.s.i. A double pigtail stent was left *in situ* for 1 to 3

months. Follow-up ultrasound or IVU was performed in both groups and extended over 2 to 37 months.

Complications occurred in 3 patients. One developed a recurrent stone and was treated by percutaneous nephrolithotomy. One needed antegrade insertion of a double pigtail stent post-operatively and 1 required a retrograde double pigtail stent after the removal of a nephrostomy tube.

All patients were pain-free at follow-up. In the short term both procedures appear to be satisfactory. Endoscopic balloon dilatation has been reserved for short PUJ strictures. The long-term results will not be available for several years. These minimally invasive techniques can be repeated if necessary and are especially useful in frail, elderly patients.

Case Reports

Rhabdomyosarcoma of the Bladder Base in Two Older Children

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Genitourinary rhabdomyosarcoma is an uncommon tumour in children, presenting at a mean age of 4.4 years (Broecker *et al.*, 1988). Two older children presenting with acute retention of urine due to rhabdomyosarcoma of the prostate/bladder neck are described.

Case Reports

Case 1. A 5½-year-old boy presented with a urinary tract infection which was treated with antibiotics, but later returned with acute urinary retention and was catheterised. His mother commented that his urinary stream had always been poor. His urine was sterile on culture. An intravenous urogram revealed normal kidneys and ureters and a lobulated filling defect in the base of the bladder. At cystoscopy there was a polypoid lesion protruding into the base of the bladder and prostatic urethra, forming a mobile mass about 2 × 2 cm in size. Histology revealed this to be an embryonic rhabdomyosarcoma. He was treated by radical cystoprostatectomy with division of the urethra at the distal sphincter and ileal conduit diversion. Histological examination of the resected specimen showed complete excision with no lymph node involvement.

Post-operatively he was treated with 6 cycles of vincristine, actinomycin-D and cyclophosphamide (VAC) and was then maintained on oral cyclophosphamide and vincristine every 6 weeks for 12 months. Beginning 2 weeks after surgery, he also received 4950 cGy of cobalt 60 radiotherapy to the pelvis. Ten years post-operatively he remains well and free from recurrence, with normal renal function.

Case 2. A 17-year-old West Indian male presented with a 3-day history of difficulty in passing urine associated with pain in the penis and lower back. His urinary stream was poor with frequency, nocturia and terminal dribbling. There was no relevant past medical or family history. On examination he was aphyrexial and in acute urinary retention. Following catheterisation the prostate was noted to be markedly enlarged, firm and tender.

His haemoglobin, urea and electrolytes were normal; a midstream specimen of urine was sterile but contained red and white blood cells. Intravenous urography revealed normal kidneys with dilated pelvicaliceal systems and ureters. The bladder base was elevated by a mass with an

irregular outline (Fig. 1). Prostatic ultrasound showed a large (10 cm) solid mass confluent with the right lobe of the prostate with an irregular surface protruding into the bladder. This finding was confirmed by cystoscopy and bimanual examination. The obstructing tissue was resected and the histological appearance was typical of an embryonal rhabdomyosarcoma (Fig. 2). Chest X-ray and



Fig. 1 Intravenous urogram with large lobulated filling defect in the bladder base (Case 2).

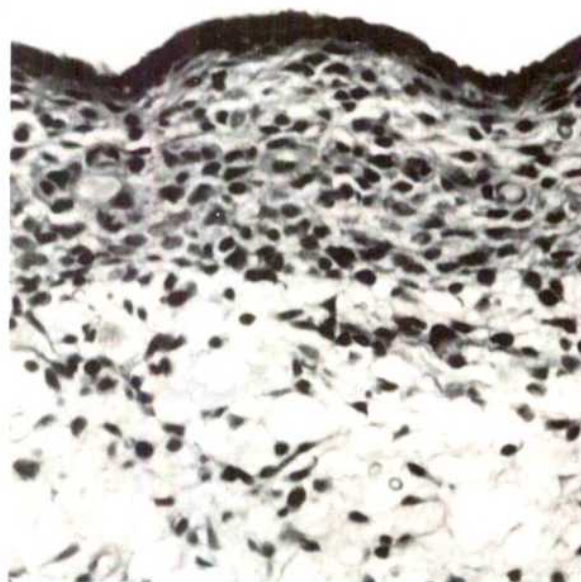


Fig. 2 The tumour cells are distributed in a cellular zone (cambium layer) beneath the intact epithelium. Underlying cells are separated by myxoid stroma. (× 100)

bone marrow biopsy were normal. CT scan showed a large mass almost filling the bladder and extending posteriorly to involve the anterior wall of the rectum (Fig. 3). There was no evidence of extravesical involvement.

He was initially treated with 4 courses of VAC alternating with vincristine, etoposide and doxorubicin; this was followed by radiotherapy to the pelvis. Tumour regression was apparent on physical examination and follow-up CT scans. He received further cytotoxic therapy which was stopped prematurely because of septicæmia. One month later he developed haematuria and a CT scan revealed further tumour growth. He subsequently underwent total cystectomy with an ileal conduit. Histology revealed involvement of a common iliac lymph node by tumour, but the cystectomy specimen consisted only of necrotic material. He died from recurrent disease 13 months after the initial diagnosis.

Comment

Rhabdomyosarcoma of the prostate and bladder neck are rare tumours; 75% of affected children (usually boys) are under 5 years of age (Broecker *et al.*, 1988). These tumours also occur in the elderly but are usually diffuse intravesical lesions and have a poor prognosis (Jones and Oberman, 1964). They seldom occur between these 2 age groups.

During the last 2 decades the emphasis on treatment of this rare tumour has changed from primary radical surgery towards aggressive chemotherapy combined with some form of local tumour

control. This may consist of radiotherapy or limited surgical excision with an attempt to preserve the bladder. Radical surgery remains the only option for those who fail to respond to or have residual disease following chemotherapy and radiotherapy. Both of our patients eventually received all 3 treatment modalities, but the order in which these treatments were given illustrates the changing philosophies governing the management of this tumour. It also highlights the difficulty in balancing the better quality of life in these young men against the bad prognosis if the tumour is not controlled by the primary treatment (Burger *et al.*, 1989).

The widely differing outcome in each case may reflect the tumour stage, histology and age of the patients. It has been suggested that DNA profiles, cytogenetic and molecular genetic analyses should be investigated to see whether they provide more accurate prognostic indicators (Lancet, 1989). However, the possibility should be considered that very bulky tumours (> 10 cm) may be relatively resistant to chemotherapy and irradiation.

With the advent of nerve-sparing cystoprostatectomy, bladder substitution and reconstruction techniques, many of the mutilating sequelae of radical surgery may be avoided. However, our first patient was not considered suitable for undiversion. It may be that with bulky tumours chemotherapy should be combined with early radical surgical excision and radiotherapy held in reserve for recurrent disease. Only further studies will answer this question.

Acknowledgement

We thank the Pathology Department, King's College Hospital, for providing the photomicrograph.

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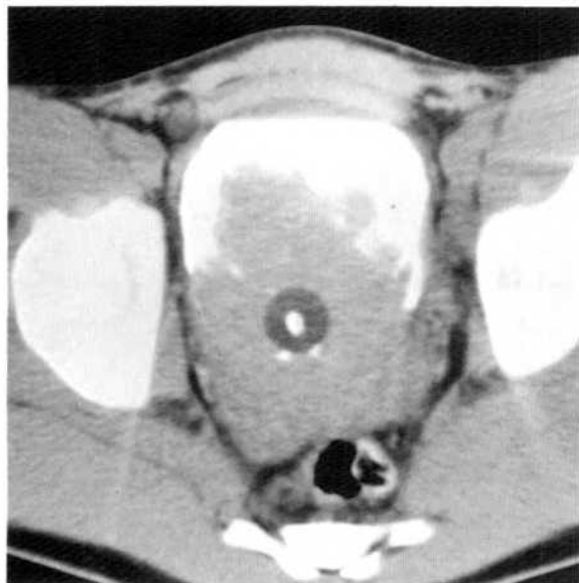


Fig. 3 CT scan with intravesical contrast revealing tumour extending into the bladder lumen (Case 2).

Pilonidal Sinus of the Penis

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Pilonidal sinus occurs most commonly in the upper part of the natal cleft. This condition is not, however, entirely limited to this site and has been reported in the axilla, sole of the foot, umbilicus, interdigital clefts, anterior chest wall, an above knee amputation stump and the perineum. We report a case affecting the penis which, although previously described, is a rare site of occurrence.

Case Report

A 24-year-old, unemployed man who was uncircumcised presented with an ulcerating lesion on the dorsum of his penis beneath the foreskin. The lesion had been present for approximately 4 years and on 2 occasions an abscess had developed at the same site and had been lanced by the general practitioner. On examination, there was a 1 × 1 cm ulcer lying in the midline on the dorsal aspect of the penis visible only on retraction of the foreskin. There was no inguinal lymphadenopathy. A circumcision was performed as the initial impression was that this may have been a carcinoma of the penis. Lying beneath the lesion, surrounded by thickened fibrous tissue, were several small dark hairs and it was at this point that the diagnosis was considered to be that of a pilonidal sinus.

The excised foreskin (6 × 2 cm) showed an irregular depressed area upon which there was an opening of a sinus track. This ran from the mucosal surface of the prepuce to open on to the dorsal aspect through a small opening 0.1 cm in diameter.

Histology revealed inflamed atypical squamous epithelium and the sinus track was lined by mature keratinising squamous epithelium with focal chronic inflammation. Keratin debris, but no hair shaft, was found in the lumen (Fig.). The appearances were of an epithelialised track compatible with pilonidal sinus.

The patient made an uneventful recovery and remains well.

Comment

Pilonidal sinus of the penis, first described by Bervar *et al.* (1968), is rare; there are 3 further reports in the literature (Yates-Bell, 1968; Fisher *et al.*, 1976; Griffin *et al.*, 1990). Our patient was similar and his presentation with recurrent abscess formation was typical. A diagnosis of penile carcinoma was considered and in 2 of the previous cases, as in ours, the hairs that were found in the sinus were not of the same colour as the scalp or

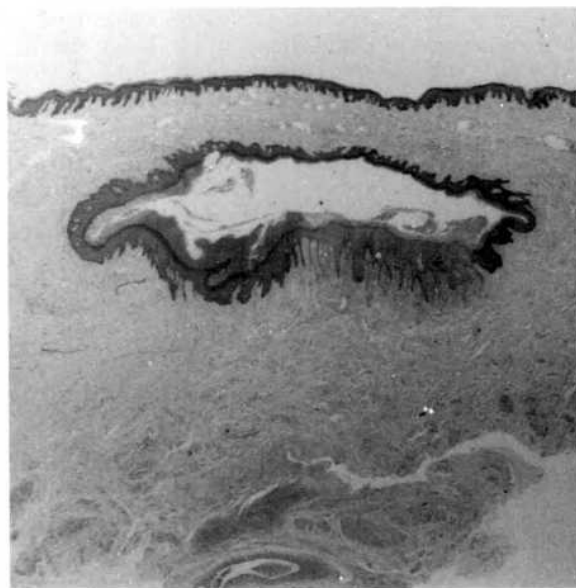


Fig. Transverse section through sinus track (H + E × 50)

pubic hair. This, together with the fact that in all cases the patient was uncircumcised, adds further support to the theory of an acquired aetiology of this condition.

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Pyeloureteritis Cystica: An Unusual Case of Haematuria in a Renal Transplant Patient

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Case Report

A 51-year-old female presented with a 3-week history of painless wholestream haematuria and no other symp-

toms. She had had a renal transplant 14 years previously for chronic renal failure, secondary to pyelonephritis, and was otherwise well.

On examination, the transplant kidney was not tender and no other abnormalities were detected. Haematological and biochemical screening was normal and urine analysis revealed pus and red cells but no growth on culture. Ultrasound showed scarred native kidneys with a normal transplanted kidney. Cystoscopy was normal and ascending ureterograms revealed multiple filling defects throughout both ureters (Fig.). Ureteroscopy showed smooth lesions along the ureteric walls and biopsy confirmed these to be cystic with the epithelial appearances of pyeloureteritis cystica. This is the first report of this condition in association with previous renal transplantation.



Fig.

Comment

Pyeloureteritis cystica, first described by Morgagni (1761), is a rare condition characterised by the formation of multiple cysts in the walls of the renal pelvis and ureter (Askari and Herrera, 1980). Most patients present with recurrent haematuria, pyuria and symptoms of infection or calculus disease, which is often an associated problem (Patch, 1939). The aetiology is uncertain, but it may evolve in relation to chronic infection and represent a metaplastic change in the urothelium (Mostofi, 1954). The natural history is unknown, although the closely related condition, cystitis glandularis, may have malignant potential (Mostofi, 1954; Edwards *et al.*, 1972).

We propose to follow this patient with regular

urine analysis and urine cytology. Intractable haematuria may necessitate bilateral nephroureterectomy of her native kidneys.

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Migration of Suprapubic Catheter to Anterior Urethra

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Insertion of a suprapubic catheter is indicated in a variety of urological situations. A case of unexpected migration of a suprapubic catheter to the anterior urethra as far as the meatus is described.

Case Report

A 30-year-old male was admitted with retention of urine. On examination he was found to have complete meatal stenosis as a result of balanitis xerotica obliterans. A K-90 catheter was inserted suprapubically through a trocar and fixed to the skin. The urethra was infected and so the patient was discharged on antibiotics and asked to return in 2 weeks' time for meatoplasty. However, he returned after 12 days because the suprapubic catheter was no longer working and urine dripped from the meatus. His penis was partially erect and the tip of the K-90 catheter could be palpated along the whole length of the urethra. The catheter was pulled back into the bladder and removed at meatoplasty.

Comment

Migration of the catheter down the urethra to the meatus was probably related to its excessive length



Fig. Ascending urethrogram showing catheter extending to the meatus.

inside the bladder and the patient's efforts to pass urine.

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Primary Malignant Melanoma of the Male Urethra

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Case Report

A 66-year-old man presented with haematuria, dysuria and symptoms of bladder outflow obstruction. It was impossible to pass a urethroscope owing to an irregular lesion of the anterior urethra. Biopsies showed an anaplastic carcinoma. Suprapubic cystoscopy showed a normal bladder but the posterior urethra could not be entered.

An anterior urethrectomy was performed and during mobilisation of the posterior urethra a further hard lesion was palpable, but instrumentation was again impossible. Finally a cysto-prostatourethrectomy and ileal conduit were performed. The patient made a good recovery and was discharged home.

Histology of both anterior and posterior urethra showed malignant melanoma with subepithelial spread. The abnormal melanocytes forming adjacent intra-epithelial tumour were typical of a primary malignant melanoma. Examination of the skin did not reveal any pigmented lesions or any evidence suggesting a regressed primary lesion.

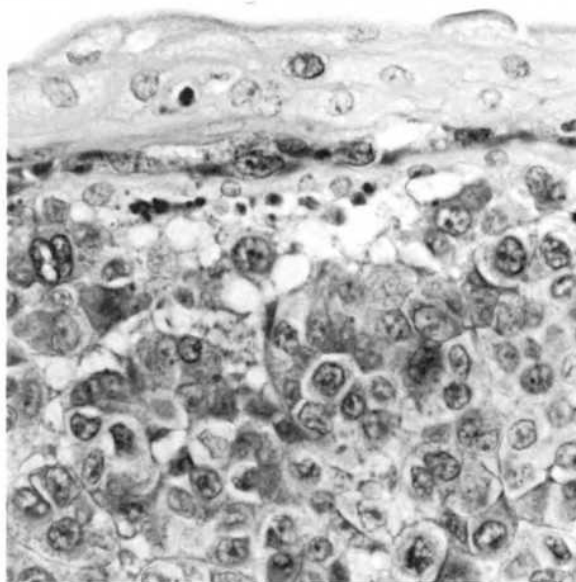


Fig. Section of male urethra at $\times 720$ stained with antibody to S100 (a marker for malignant melanoma cells). A row of stained melanoma cells is shown deep in the stratified urothelium and scattered melanoma cells more superficially in the epithelium. These appearances are typical of primary malignant melanoma.

Comment

Primary malignant melanoma of the male urethra is very rare. The majority are located in the fossa navicularis and distal urethra, with only 20% in the proximal urethra. In this case the tumour was undoubtedly confined to the proximal urethra, while many of the reported distal cases represent spread from the glans penis (Weiss *et al.*, 1982). Only 26 cases have previously been reported in the literature (Pow-Sang *et al.*, 1988). Despite aggressive therapy in the form of cysto-prostatourethrectomy, male patients have a very poor prognosis. The majority die of tumour-related disease or develop metastases within 3 years; only 3 five-year survivors are reported (Petersen, 1986).

Acknowledgements

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Primary Carcinoid of the Bladder

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Case Report

A 61-year-old female presented with persistent asymptomatic microscopic haematuria, detected on routine urine microscopy. Urine culture was negative and intravenous urography normal. Cystoscopy revealed a 3-mm red papillary lesion on the trigone which was resected transurethrally. Histopathological examination revealed a 2-mm fragment containing no transitional epithelium, polygonal cells with granular eosinophilic cytoplasm and regular nuclei. The appearances were those of a benign endocrine cell (carcinoid) tumour (Fig.). Two subsequent check cystoscopies, chest X-ray, ultrasound scan of liver and urine 5-hydroxyindoleacetic acid levels were all normal.

Comment

It is over 50 years since neuro-endocrine cells have been recognised as occurring in the urinary bladder and during this time only 2 cases of primary carcinoid of the bladder have been described (Colby, 1980; Yang *et al.*, 1985). Colby's reported case was similar to ours; the tumour was small, benign, situated on the trigone and diagnosed only on histopathological examination following transurethral resection.

The main differential diagnosis for these endocrine tumours is that of pheochromocytoma, which

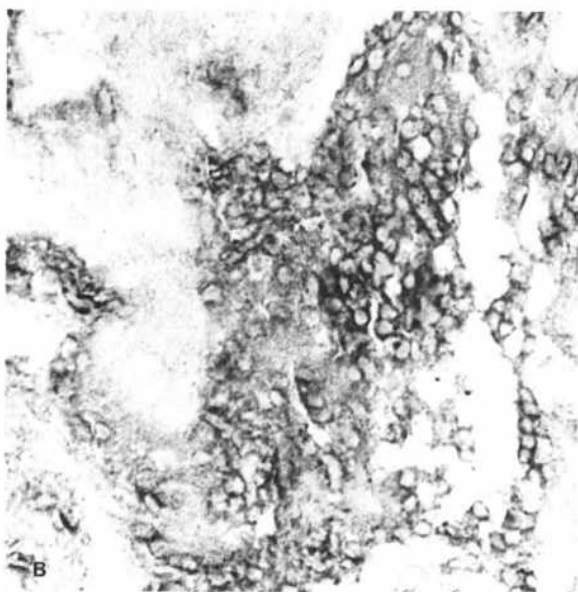
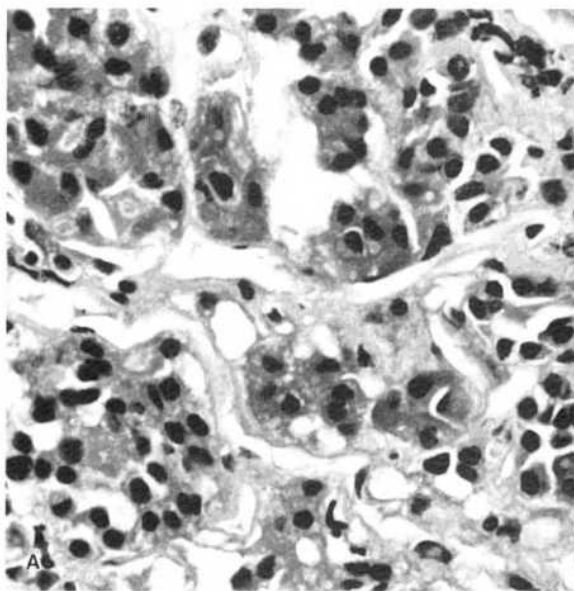


Fig. (A) Histological appearance of tumour in biopsy showing groups of polygonal cells with regular nuclei and abundant granular cytoplasm. (H and E $\times 300$). (B) Tumour stained to show cytoplasmic argyrophilic granules. (Gremelius stain $\times 300$).

accounts for 0.06% of all bladder tumours (Leestma and Price, 1971). Light microscopy is usually sufficient for diagnosis, but if this is equivocal, electron microscopy can be used to study the ultrastructure, in particular the distribution of dense core granules. Although pathology suggested a benign primary carcinoid bladder tumour, a

primary tumour in the more usual sites, namely the gastrointestinal tract or lungs, was excluded.

Primary carcinoid of the bladder should be included in the list of rare bladder tumours together with phaeochromocytoma, adenocarcinoma, metastatic lesions, inverted papilloma and ectopic prostatic tissue.

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Severe Haemorrhage after Extracorporeal Shock Wave Lithotripsy: Radiological Evaluation

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Case Report

A 52-year-old female underwent extracorporeal shock wave lithotripsy (ESWL) (Siemens Lithostar, 3500 shocks at 16.6 kV) for a non-obstructing 10 × 5 mm renal pelvic calculus. The patient denied medications, bleeding disorders (normal coagulation measurements) and hypertension.

Acute, severe flank pain developed 2 h post-operatively. Vital signs and haemoglobin were initially stable. Voided urine revealed the typical gross haematuria after ESWL. The left psoas shadow was not visible on plain abdominal X-ray (Fig. 1). Renal ultrasonography was non-diagnostic. In contrast, an abdominal computed tomography (CT) scan revealed a large left perirenal haematoma (Fig. 2).

She eventually required 1 unit of blood after her haemoglobin reached a nadir of 8.6 g/dl. Pain was controlled within 48 h with oral medication. A 5-month follow-up CT scan revealed a fully recovered, normal left kidney.

Comment

The acute onset of severe flank pain after ESWL should arouse suspicion of obstructing stone fragments, blood clots or internal haemorrhage. Newer,



Fig. 1 KUB X-ray after ESWL showing fragmentation of the calculi and absence of the psoas shadow on the patient's left side.

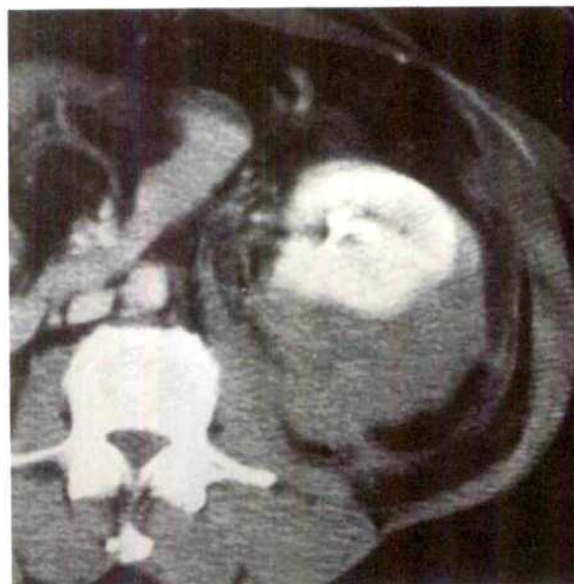


Fig. 2. CT scan after ESWL treatment accurately staging a large left perirenal haematoma.

less powerful lithotriptors can still cause severe injury. Post-lithotripsy haematuria is expected; its severity does not correlate with internal injury. In contrast, severe flank pain unresponsive to traditional analgesics is unusual and may represent life-threatening haemorrhage (Stoller *et al.*, 1989).

Initial haemoglobin values may remain unchanged despite significant haemorrhage. Renal ultrasonography may not detect the injury. Appropriate evaluation requires abdominal CT imaging, as in our patient (Fig. 2), to stage the injury and direct a management plan that must include in-patient monitoring, fluid resuscitation and possible blood transfusions. Out-patient lithotripsy requires observation and monitoring to ensure adequate recovery prior to discharge.

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Urothelial Tumour of Renal Pelvis in Patient with Crossed Ectopia

S. LIU, H. LEUNG and J. CONSIDINE, *Department of Urology, East Birmingham Hospital, Birmingham*

Case Report

A 74-year-old man presented with 2 episodes of frank painless haematuria. He had no other urinary symptoms and physical examination was normal. Intravenous urography showed a low-lying, left-to-right, crossed fused ectopia (Weiss and Mills, 1989) which appeared to have an ill defined 2-cm filling defect of the inferomedial pelvis (Fig. 1). This was subsequently confirmed by retrograde pyelography performed via the "left" ureteric orifice (Fig. 2). A provisional diagnosis of renal pelvic tumour was made, although urine cytology was negative. In order to delineate the vascular anatomy of this ectopic kidney, pre-operative aortography and selective renal angiography were carried out (Fig. 3).

An anterior transperitoneal exploration of the kidney was performed followed by hemi-nephroureterectomy of the lower moiety of the fused kidney and its draining ureter. Histology of the renal pelvic tumour confirmed a grade II transitional cell carcinoma with no evidence of muscular invasion. There was no clinical or operative evidence of metastatic disease.

Comment

Crossed fused renal ectopia is a rare congenital anomaly which has an autopsy incidence of 1 in



Fig. 1 Intravenous urogram showing low-lying, left-to-right, crossed fused ectopia and an ill defined filling defect of the inferomedial pelvis of the fused kidney.

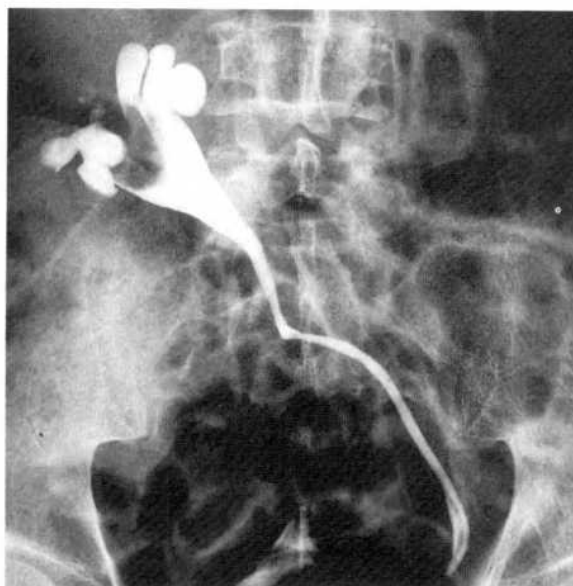


Fig. 2 Retrograde pyelogram via the crossed ureter confirming a space-occupying lesion of the inferomedial pelvis of the fused kidney.

2000. It is probably produced by abnormal development of the ureteric bud (Marshall and Friedman, 1978). The incidence of urothelial tumour in crossed ectopia is unknown and the association has not been reported previously.

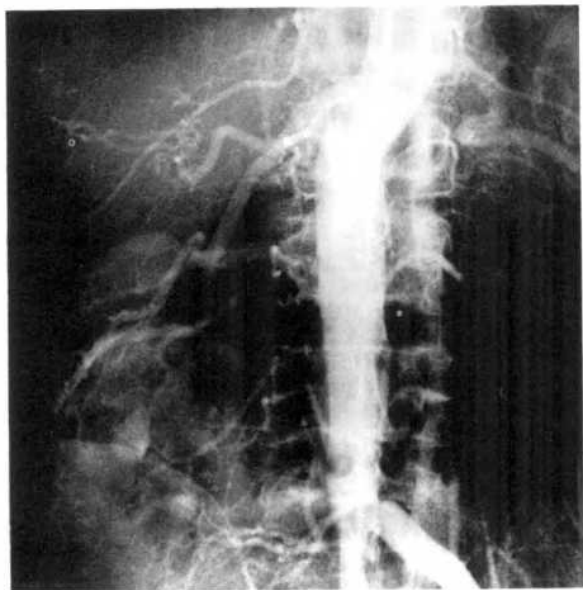


Fig. 3 Aortogram showing the anomalous blood supply to the crossed ectopic kidney.

References

- Marshall, F. F. and Freedman, M. T.** (1978). Crossed renal ectopia. *J. Urol.*, **119**, 188.
- Weiss, M. A. and Mills, S. E.** (1989). Anomalies of the urinary tract. In *Atlas of Genitourinary Tract Disorders*. Volume II. Chapter 4, section 10. London: Gower Medical.

Requests for reprints to: S. Liu, Department of Urology, East Birmingham Hospital, 45 Bordesley Green East, Birmingham B9 5ST.

Point of Technique

Harpoon Device for Removal of Obstructed Balloon Catheters

K. J. O'FLYNN, D. G. THOMAS and A. HARDY, *Spinal injuries Unit, Lodge Moor Hospital, Sheffield*

We describe a method of removing obstructed balloon catheters. The method is safe and simple and does not require an anaesthetic.

Technique

The end of the catheter is cut and a well lubricated cystoscope sheath is passed over the catheter and down the shaft of the penis. Gentle traction is applied to the catheter until it abuts the end of the cystoscope sheath. A harpoon (comprising the sharpened end of a catheter introducer) is passed down the sheath to burst the catheter balloon and the catheter is then withdrawn (Fig.). The patient later has a cystoscopy to ensure that there are no retained fragments in the bladder.

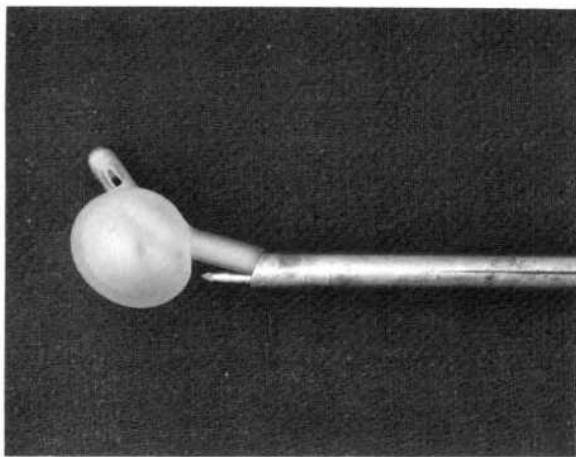


Fig. Harpoon device.

Comment

Failure of a balloon catheter to deflate is not uncommon. Various methods have been recommended, including traction, hydrostatic distension and chemical dissolution. Instillation of either ether or chloroform may cause a chemical cystitis and

retained fragments are common and therefore this technique is not recommended. Transcatheter puncture using a ureteric catheter is frequently successful (Sood and Sahota, 1972), but on occasion the wire stylet cannot be negotiated down the inflation channel of the catheter. Percutaneous balloon rupture usually necessitates either ultrasound or radiological control and a local or general anaesthetic (Moisey and Williams, 1980; Chin *et al.*, 1984). The harpoon device is safe and has been used over the past 20 years in this hospital with no complications.

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- Chin, P. L., Singh, R. K. and Athey, G. (1984). Removal of retained urinary catheters. *Br. J. Urol.*, **56**, 185–187.
Moisey, C. U. and Williams, L. A. (1980). Self-retained balloon catheters—a safe method of removal. *Br. J. Urol.*, **52**, 67.
Sood, S. C. and Sahota, H. (1972). Removing obstructed balloon catheter. *Br. Med. J.*, **4**, 735.

Request for reprints to: K. J. O'Flynn, Spinal Injuries Unit, Lodge Moor Hospital, Redmires Road, Sheffield S10 4LH.

Endoscopic Management of the Undeflatable Foley Catheter Balloon

A. SAXENA, S. KHANNA and B. K. VOHRA *Department of Urology, Sir Ganga Ram Hospital, New Delhi, India*

Various methods have been described for deflating the balloon of an indwelling urethral catheter (Pearman, 1960; Lutin and Mullins, 1982; Moffat *et al.*, 1986; Vandendris, 1986).

We have successfully used the following endoscopic technique for puncturing the balloon under vision.

A paediatric cystourethroscope (we use a 12F sheath) or, if that is not available, a 15.5F sheath is passed *per urethram*, under vision, by the side of the catheter. There is no trauma to the urethra as the opposing walls of the catheter collapse with the advancing cystourethroscope.

Once inside the urinary bladder the balloon is easily visualised. A coagulating electrode is then introduced through the side channel and the surface of the balloon is given short bursts of diathermy under vision. The cystoscope is then removed followed by the urethral catheter.

It is seldom possible to puncture the balloon with a guide wire introduced via the side channel of cystoscope as it is difficult to fix the balloon.

We have used this technique where hydrodistension, probing with a wire stylet and chemical dissolution have failed. This method has the advantage of being simple, safe and quick. Perhaps the most important point of differentiation from the usual techniques is that there is no unpredictability with this technique since all manoeuvres are carried out under vision.

References

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 Moffat, L. E. F., Teo, C. and Dawson, I. (1986). Ultrasound in the management of undeflatable Foley catheter balloon. *Urology (Suppl.)*, **27**, 25.
 Pearman, R. O. (1960). Balloon catheter which will not deflate. Simple method of puncturing balloon. *J. Urol.*, **84**, 438.
 Vandendris, M. (1986). How to deflate refractory balloon of a bladder catheter. *Urology (Suppl.)*, **27**, 27.

Requests for reprints to: A. Saxena, C-26 Hauz Khas, New Delhi - 110 016, India.

Partial Nephrectomy Using a Linear Stapling Device

J. BANIEL and M. SCHEIN, *Department of Urology and Surgery, Hillbrow Hospital and University of the Witwatersrand, Johannesburg, South Africa*

The use of linear stapling devices is well entrenched in gastrointestinal surgery but not in operations on solid organs (Patcher *et al.*, 1979; Raschbaum *et al.*, 1988; Voyles and Vogel, 1989). Our experience with linear staplers during partial splenectomy and resection of the left lobe of the liver prompted us to use this technique in partial nephrectomy.

Case Report

A 38-year-old male patient was admitted following a gunshot injury to the right upper quadrant of the abdomen. He was haemodynamically unstable, with a rigid abdomen and haematuria. At immediate laparotomy, laceration of the liver and an expanding perinephric haematoma were noted. After suture control of the hepatic bleeding, the right renal pedicle was controlled and the kidney exposed; a major laceration of the apical

pole, with extravasation of urine, was found. The 2 segmental arteries supplying the injured upper pole were ligated. A linear stapling device (TA-55, 4.8 mm, Auto Suture Co., UK) was applied across the healthy renal tissue and capsule inferior to the laceration and activated. The injured pole was resected beyond the double row of staggered stainless staples, resulting in immediate haemostasis. A pedicle flap of omentum was sutured to the cut edge of the kidney. The partial nephrectomy required 15 min. The post-operative course was uneventful, with no urinary drainage through the suction drain, which was removed on the second post-operative day. Follow-up intravenous urography demonstrated a sharply defined cut surface of the upper pole with excellent function and no extravasation of urine.

This case demonstrates the ease and speed of partial nephrectomy using a linear stapling device, but further studies are warranted to establish its role in partial renal resection.

References

- Patcher, H. L., Pennington, R., Chassin, J. *et al.* (1979). Simplified distal pancreatectomy with the Auto Suture stapler: preliminary clinical observations. *Surgery*, **85**, 166-170.
 Raschbaum, G. R., Harner, T. J. and Canizro, P. C. (1988). The use of stapler in splenic salvage as an alternative to the sutured partial splenectomy or splenorrhaphy. *Surg. Gynecol. Obstet.*, **166**, 179-180.
 Voyles, C. R. and Vogel, S. B. (1989). Hepatic resection using stapling devices to control the hepatic veins. *Am. J. Surg.*, **158**, 459-460.

Requests for reprints to: M. Schein, Department of Surgery, Medical School, York Road, 2193 Parktown, Johannesburg, South Africa.

Urethroplasty for Condylomata Acuminata throughout the Urethra

M. R. FENELEY, S. LIU, P. D. MILLER and R. S. KIRBY, *Department of Urology, St Bartholomew's Hospital, London*

Case Report

A 26-year-old West Indian man had a 5-year history of recurrent condylomata acuminata affecting the external genitalia. Warts at the external meatus had become progressively more florid and extensive despite treatment with podophyllin and excision of the larger lesions under general anaesthesia. Endoscopy showed extensive involvement of the entire urethra. The penile and bulbar urethra was laid open on its ventral aspect to facilitate direct control of the lesions and serve as the first part of a 2-stage urethroplasty (Fig.). The condylomata were



Fig. Ventral penile surface after the urethra has been laid open.

excised under direct vision and further recurrences were treated by excision and topical application of 5%

5-Fluorouracil (5-FU). Second-stage urethroplasty will be carried out when the condylomata have been eradicated.

Comment

Urethroscopy in patients with recurrent or extensive meatal warts may reveal significant urethral involvement. The treatment of multiple urethral lesions by endoscopic resection and fulguration is often followed by recurrence and sometimes by stricture formation. Furthermore, condylomata may be spread proximally by endoscopy (Dretler and Klein, 1975). Chemotherapy applied via the external meatus may cause an acute urethritis and even precipitate urinary retention. In addition, adequate topical exposure cannot be guaranteed proximal to the external sphincter.

Local treatment may be facilitated by perineal urethrostomy (Cetti, 1984) or by opening the anterior urethra (Debenedictis *et al.*, 1977). However, when the entire urethra is involved, 2-stage urethroplasty of the bulbar and penile urethra permits good access for excision and the topical application of chemotherapeutic agents without the need for repeated endoscopic procedures.

References

- Cetti, N. E. (1984). Condyloma acuminatum of the urethra: problems in eradication. *Br. J. Surg.*, **71**, 57.
- Debenedictis, T. J., Marmar, J. L. and Praiss, D. E. (1977). Intraurethral condylomas acuminata: management and review of the literature. *J. Urol.*, **118**, 767-769.
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Requests for reprints to: M. R. Feneley, Department of Urology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

Correspondence

Dear Sir,

re Cobb's collar—a forgotten entity. D. Cranston *et al.* *Br. J. Urol.*, **66**, 294–296, 1990.

The above article unfortunately perpetuates the urological myth of Cobb's collar. What is really being demonstrated in the X-ray (Fig. 2) is indentation of the urethra by a contraction of the musculus compressor nuda and is a normal finding. It is well described in the uro-radiology literature (McCallum. *Radiol. Clin. North Am.*, **17**, 227–244, 1979; O'Reilly *et al.* (eds). *Diagnostic Techniques in Urology*. P. 19. Philadelphia: Saunders. 1990; Dunwick *et al.* (eds). *Textbook of Uroradiology*. P. 7. Baltimore: Williams and Wilkins. 1991).

Yours faithfully,

J. N. Corriere
Division of Urology, Texas Medical Center, Houston, USA

Reply by D. Cranston *et al.* Professor Corriere describes Cobb's collar as a urological myth. Those urologists who routinely urethroscopically their male patients will be aware of the occasional presence of a fine diaphragmatic structure which is endoscopically clearly not due to muscular spasm.

Instrumentation by disrupting this diaphragm may well aggravate the problem and we are in the process of preparing a paper in which several patients have developed a complete obstruction of the urethra at this site, a phenomenon not usually associated with muscular spasm. In addition, internal urethrotomy on these severely obstructed patients will often completely relieve the urinary difficulty, indicating this is a true obstruction.

Dear Sir,

re Treatment of recurrent urethral strictures using clean intermittent self-catheterisation. G. S. M. Robertson *et al.* *Br. J. Urol.*, **68**, 89–92, 1991.

Further to the above paper, we would additionally like to acknowledge the help we received from the Department of Urology in Nottingham with the

initial protocol used in this study and their previous publication on this subject (W. T. Lawrence and R. P. MacDonagh. *J. R. Soc. Med.*, **81**, 136–139, 1988). We apologise for our initial oversight in failing to do so.

Yours faithfully,

G. S. M. Robertson, N. Everitt, J. R. Lamprecht, M. Brett and J. T. Flynn
Area Urological Service, General Hospital, Leicester.

Dear Sir,

re Reduction of paraphimosis. T. C. Waters and V. Sripathi. *Br. J. Urol.*, **66**, 666–667, 1990.

The authors should be complimented on bringing this technique into the open as it is both simple and effective. I have been using it for several years with very good results. However, I wish to point out that it is not as simple a procedure as it is made out to be, especially in children. Giving a penile ring block in a reluctant child must be difficult, apart from the psychological trauma involved. Furthermore, a certain amount of pressure is required to squeeze out the oedema fluid. This is not a very pleasant experience for an adult, let alone a child. Based on my experience, I have given up this technique in children. A short general anaesthetic is sufficient to reduce the paraphimosis using pressure alone; punctures are rarely required then. However, it remains an excellent procedure in adults.

Finally, it is time that concepts such as using ice packs and making dorsal slits as primary procedures for paraphimosis are deleted from the textbooks—the former because of its inconvenience and the latter because it is unnecessary and not without complications. It is always possible to reduce any paraphimosis by pressure alone or by puncture.

Yours faithfully,

A. Saxena
Department of Urology, Sir Ganga Ram Hospital, New Delhi, India.

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21–26 June 1992

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1991. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 10th January 1992.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Scholarships for Experimental and Clinical Research in Urology

The European Association of Urology and the European Board of Urology will award three scholarships for research in Urology. Each scholarship will be awarded for one year, starting on 1 July 1992, at a maximum of 33,000 ECU at any appropriate institution in the world. Further information from: The European Board of Urology Education Committee, P.O. Box 25285, 3001 HG Rotterdam, The Netherlands. Tel: 31.10.436.6665. FAX: 31.10.436.6669.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

British Journal of Urology Travelling Fellowship

This fellowship of £1500 enables a Senior Registrar or numbered Career/Research Registrar to attend the Annual Meeting of the American Urological Association. It is awarded in April each year at the Annual Scientific Meeting of the Senior Urological Registrars Group (SURG). The award is given for the best paper presented at this meeting on a vote by the members of SURG present at the meeting. Invitations to the meeting are sent out in January by the Chairman of the Senior Urological Registrars Group and papers must be new work not previously published and not resulting from a thesis. An additional Fellowship may be awarded at the discretion of the British Journal of Urology and the Senior Urological Registrars Group.

Lewis Medical Travelling Scholarship

The scholarship covers travel, accommodation and registration expenses associated with attending the Annual Meeting of the American Urological Association. The scholarship will be available to any person appointed to a numbered urological training post and will be awarded to the person presenting the winning paper at the Annual Meeting of the Senior Urological Registrars Group. An additional scholarship may be awarded at the discretion of the Senior Urological Registrars Group and Lewis Medical Limited.

Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000 to support a clinical research project. Applicants

should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. The prize will be awarded at the Annual Meeting of the Association.

Canadian Urological Association Meeting

Winnipeg, Canada. 21–25 June 1992

Further particulars from: Dr Denis H. Hosking, GE-446, 700 William Avenue, Winnipeg, Manitoba R3E 0Z3, Canada.

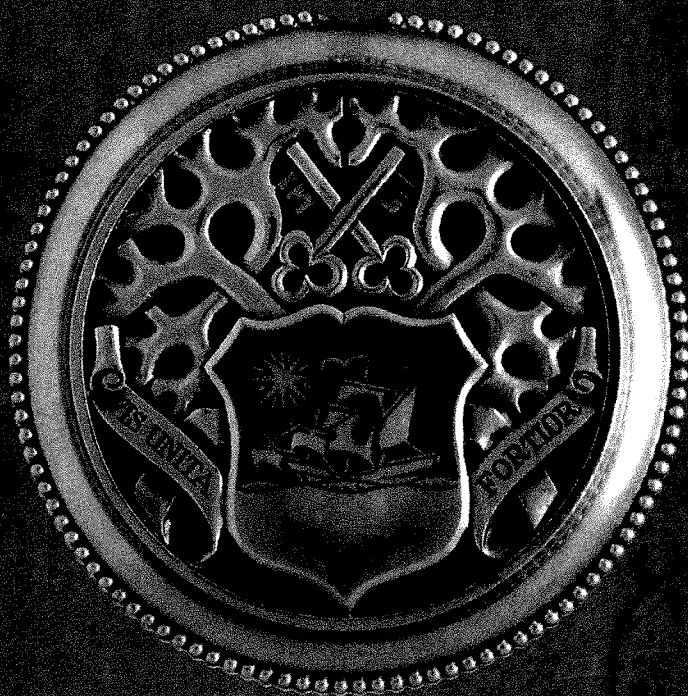
Diary

1992

- March 8–13 19th Biennial Congress of the Urological Association of South Africa, Sun City, South Africa. Contact: Dr I. Lissos, 1 Esselen Towers, Esselen Street, Hillbrow, 2001, South Africa.
- March 19–21 Eleventh International Symposium of Operative Andrology. Istanbul, Turkey. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
- March 19–21 Searching for Prostatic Carcinoma: the Problem of Screening and Early Detection. Munich, Germany. Contact: D. Née, Secretariat, Department of Urology Krankenhaus der Barmherzigen Brüder, Romanstr. 93, W-8000 Munich 19, Germany. Tel: 89/1793-252 or 89/17 56 61. FAX: 89/1782653.
- March 26–27 Eighth Annual Symposium on Progress in Paediatric Surgery, Oviedo, Spain. Contact: Dr J. L. Teixidor de Otto, Servicio de Cirugía Pediátrica, Hospital Central de Asturias, Centro Universitario, E-33006 Oviedo, Spain.
- April 3–5 Third International Conference on Geriatric Nephrology and Urology. Toronto, Canada. Contact: Dr D. G. Oreopoulos, Peritoneal Dialysis Unit, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8. Tel: 416 364 9974. FAX: 416 360 8127.
- April 9–11 6th International Urological Symposium. Girne, North Cyprus. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
- April 24–25 Annual Meeting of the Irish Society of Urology. University of Limerick. Contact: Honorary Secretary, Irish Society of Urology, at the Royal College of Surgeons in Ireland, 123 Saint Stephen's Green, Dublin 2, Ireland.
- April 25 HIV: 1992. University of California Davis Medical Center, Sacramento, USA. Contact: Office of Continuing Medical Education, UC Davis Medical Center, 2701 Stockton Boulevard, Sacramento, CA 95817, USA. Tel: (916) 734-5390. Fax: (916) 736-0188.
- May 6–8 8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.
- May 10–14 American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
- May 23–24 Société Belge d'Urologie: 57th Congress. Liège, Belgium. Contact: Dr F. F. Wart, 4 Avenue du Bois des Sartis, B-6111 Landelies, Belgium.
- May 24–28 Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.
- June 4–6 Fourth International Meeting of Andrology, Como, Italy. "Treating Male Infertility: New Possibilities". Contact: Dr G. M. Colpi, II Divisione di Chirurgia, Centro di Andrologia e Infertilità, Ospedale "VALDUCE", Via Dante 11, I-22100 Como, Italy.

- June 10–12 Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.
- June 22–25 Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
- June 23–26 BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
- July 22–25 European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
- August 7–9 Ninth Meeting of International Society for Dynamics of the Upper Urinary Tract. Akita, Japan. Contact: Dr Seigi Tsuchida, Department of Urology, Akita University School of Medicine, 1-1-1 Hondo, Akita, 010 Japan. FAX 81-188-36-2619.
- August 24–27 Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
- August 24–27 VIIth International Symposium on Urolithiasis and Related Clinical Research. Cairns, Australia. Contact: Dr Rosemary L. Ryall, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia 5042.
- September 3–6 Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
- September 14–18 Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
- October 9–10 BAUS Autumn Meeting, Swansea. Contact BAUS Office.
- December 4–5 Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.
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- May 16–20 American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
- June 20–24 Canadian Urological Association Annual Meeting, Bonaventure Hotel, Montreal, Quebec. Contact: To be announced.
- 1994
- May 15–19 American Urological Association, Moscone Centre, San Francisco, California.

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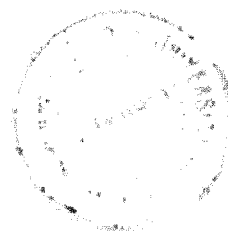
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Morris, J. A., Oates, K. and Staff, W. G. (1986) Scanning electron microscopy of adenomatoid tumours. *Br. J. Urol.* 58, 183-187.

References to books should be as follows:

Wright, F. S. and Howards, S. S. (1981). Obstructive injury. In *The Kidney*, ed. Brenner, B. M. and Rector, F. C. Second edition. Volume II. Chapter 38, pp. 2009-2044. Philadelphia: Saunders.

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REVIEW

Haemospermia

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Haemospermia is a frightening symptom. Many cases are of benign aetiology but 5 to 10% will have underlying malignancy. Many younger patients require only routine clinical examination, urine analysis and reassurance, but patients aged over 40 years, those with persistent haemospermia, or those with associated haematuria require urological investigation. Imaging of the prostate and seminal vesicles with transrectal ultrasound is of particular value in the investigation of these patients.

The presence of blood in the semen (haemospermia) has always been a neglected subject. It is rarely a serious threat to the health and wellbeing of the patient and so is often regarded by the clinician as a symptom of little significance. However, the patient is often fearful of cancer (Murphy and Weiss, 1985) and concerned about the disturbance in his sexual life.

Haemospermia is considered an uncommon symptom (Etherington *et al.*, 1990) but a busy urologist may see more than one case of haemospermia per month. The prevalence is unknown, since there may be many more unnoticed cases of haemospermia in the community. Transient haemospermia may not be observed by the patient or his partner. It can present alone or with any other urological symptom such as haematuria.

History

Haemospermia has been known for centuries and an early comprehensive article on this subject was by Hugues in 1894 (Marshall and Fuller, 1983), who noted that Hippocrates, Ambroise Paré, Morgagni, Valpeau, Fournier, Guyon and many others had seen cases. Galen also mentioned haemospermia (Parker, 1942). Lydston from the United States reported 5 cases of haemospermia in 1894 and

Jonathan Hutchinson in 1898 recorded 2 (Ross, 1969). Two more recent comprehensive reviews are by Ross (1969) and Fletcher *et al.* (1981).

Aetiology

Ross (1969) divided the causes of haemospermia into 3 groups:

- (1) Haemospermia due to definite pathological conditions.
- (2) Haemospermia due to so-called "functional" conditions.
- (3) "Essential" or "idiopathic" haemospermia.

Until the middle of the present century, functional causes were considered the most common (Pryor, 1985). These included excessive sexual indulgence or "over use" (Parker, 1942), prolonged sexual abstinence, interrupted coitus and "unbridled licence" (Ross, 1969).

"Essential haemospermia" was then considered to be common but it became clear that the patients had not been investigated thoroughly (Pryor, 1985). It would appear that in most of these cases the bleeding comes from the seminal vesicles rather than the prostate and it has been suggested that sudden emptying of a distended vesicle causes haemorrhage "*ex vacuo*" analogous to the bleeding that occurs after decompression of a chronically distended bladder (Parker, 1942; Ross, 1969).

Fletcher *et al.* (1981) and Fuse *et al.* (1988) considered that 14% and 33% respectively of their patients had "essential haemospermia". With the increasing use of transrectal ultrasound and other imaging techniques the number of cases described as "functional" or "essential" should reduce further.

The causes of haemospermia are listed in relation to age, prevalence and clinical significance (Tables 1 and 2). Rarer causes have also been listed (Table 3). It is interesting to note that even in areas where schistosomiasis is endemic, haemospermia has been shown to be due to other causes (Elem and Patil, 1982). In short, benign conditions are the most frequent causes, particularly in the younger age group, but unsuspected malignancy may occur in older men. Persistent haemospermia over a number of months is more likely to be due to a detectable underlying pathology than simply due to inflammation or to be idiopathic in nature.

Investigations

It is important to take a careful history. This will help to distinguish haemospermia from urethral bleeding. It is said that bleeding from the posterior urethra is pink or red, whereas blood originating in the seminal vesicles or the prostate is dark (Ross, 1969). Haemospermia should also be differentiated from the extremely rare melanospermia reported to occur in patients with metastatic malignant melanoma (Smith *et al.*, 1980). This can be done by

Table 1 Causes of Haemospermia in Young Men (<40 years)

Inflammatory
Prostatitis
Seminal vesiculitis
Urethritis
Epididymo-orchitis
Benign seminal vesicular and prostatic lesions
Dilatation of seminal vesicle
Cysts (Heller and Whitesel, 1963)
Diverticula or lobulation (Yada, 1963)
Calculi (Widdison and Feneley, 1989) or calcification (Yada, 1963)
Benign urethral lesions
Granulations or papillary adenomata or adenomatous polyps
Abnormal veins in prostatic urethra
Haemangioma of urethra (Yu <i>et al.</i> , 1977)
Condylomata acuminata or urethral warts
Urethral stricture
Tumours
Seminal vesicle
Leiomyoma
Carcinoma (Smith <i>et al.</i> , 1967)
Testis (Pryor, 1985)

Table 2 Causes of Haemospermia in Older Men (>40 years)

Tumours
Prostate
Carcinoma
Sarcoma (Tripathi and Dick, 1969)
Intraductal carcinoma
Bladder
Seminal vesicle
Carcinoma
Leiomyoma
Urethra
Benign prostatic and seminal vesicular lesions
Benign prostatic hyperplasia
Calculi or calcification
Dilatation of seminal vesicle
Diverticula or lobulations
Benign urethral lesions
Granulations or papillary adenomata or adenomatous polyps
Abnormal veins in prostatic urethra
Haemangioma of urethra
Urethral stricture
Inflammatory
Prostatitis
Seminal vesiculitis
Epididymo-orchitis
Urethritis
Hypertension

Table 3 Rarer Causes of Haemospermia

Urinary tract calculi
Urethra
Bladder
Ureter
Bleeding diathesis
Haemophilia (Yu <i>et al.</i> , 1977)
Purpura
Leukaemia
Scurvy
Trauma
Testis (including post-orchectomy)
Perineum (Tolley and Castro, 1965)
Including repeated compression (Marshall and Fuller, 1983)
Post-haemorrhoidal injection
Traumatic Peyronie's disease
Amyloidosis of seminal vesicle
Semino-vesico-venous fistula
Ossified vas at junction with seminal vesicle
Utricular cyst (Van Poppel <i>et al.</i> , 1983)
Tumours of spermatic cord and prostatic utricle
Pelvic malignancy
Lymphoma (Geoghegan and Bonavia, 1990)
Haemorrhoids
Cirrhosis of liver
Sexually transmitted diseases
Gonorrhoea
Syphilis
In endemic areas
Bilharziasis
Tuberculosis

chromatography (Leary and Aguilo, 1974). The patient should be asked about the duration of symptoms and the type and frequency of haemospermia. In a recent series by Jones (1991), most men (75.5%) had experienced only 1 or 2 episodes of haemospermia at the time of consultation. The presence of other urological symptoms should be noted and their presence may dictate further management.

In a series by Fletcher *et al.* (1981) 39% had haemospermia, only 20% had haematuria as well and the remainder had a variety of additional symptoms such as dysuria, ejaculatory pain, prostatism or testicular, perineal or suprapubic discomfort.

Clinical examination sometimes helps to localise the source of bleeding. It includes careful examination of the testes, the epididymes and the spermatic cords. Digital rectal examination of the prostate and the seminal vesicles should be undertaken and the external urinary meatus should be inspected after the rectal examination so that any discharge can be assessed. The presence of genital warts should be noted and hypertension should be excluded.

Initial investigation includes urine collection (preferably after prostatic massage) for microscopy and routine culture, and urine cytology (in older men). A plain radiograph of the abdomen (KUB) will visualise calcification in the prostate and seminal vesicles or urinary tract calculi. Seminal analysis may be considered and was abnormal in 54% of patients in the series by Fletcher *et al.* (1981).

An intravenous urogram (IVU) is rarely contributory in the investigation of haemospermia. Only 6% of IVUs showed abnormalities in the series by Fletcher *et al.* (1981). It should be considered only if the patient has had frank or microscopic haematuria. It is also to be noted that abnormalities detected on the urogram are not necessarily the cause of haemospermia (Pryor, 1985).

Transrectal ultrasound (TRUS) has improved the investigation of haemospermia. It is a simple, safe, effective and relatively non-invasive outpatient method of objectively assessing the prostate and seminal vesicles. In a series by Etherington *et al.* (1990), TRUS was abnormal in 83% of patients with haemospermia. Hence it should be considered the most important imaging technique necessary to investigate patients presenting with haemospermia in the absence of other symptoms. Suspicious lesions on transrectal ultrasound can be biopsied at the same time under ultrasound guidance. In our

own on-going study, 20 consecutive patients with haemospermia have undergone transrectal ultrasound. Five patients had abnormalities of the seminal vesicles, including dilatation (Fig. 1), atrophy, cyst formation and asymmetry. In 3 cases there were hypoechoic lesions in the prostate which were biopsied. Two of these revealed carcinoma of the prostate (Fig. 2) and both patients have subsequently undergone nerve-sparing radical

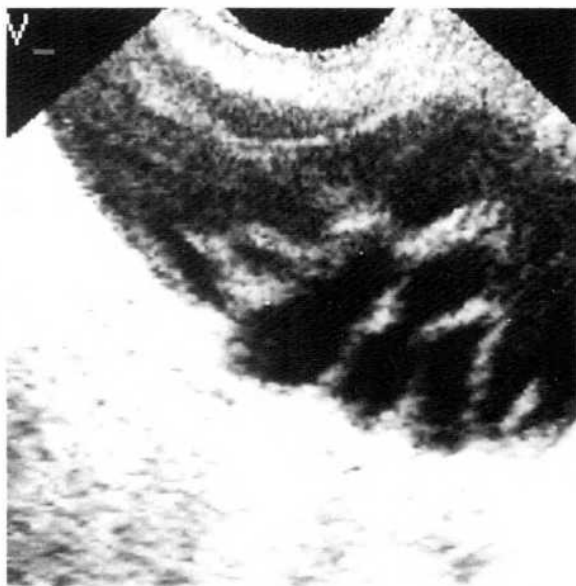


Fig. 1 Transrectal ultrasound showing seminal vesicular dilatation.

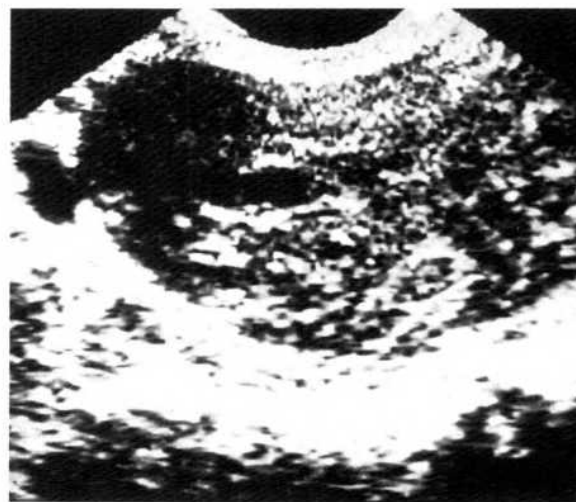


Fig. 2 Transrectal ultrasound showing hypoechoic lesion which biopsy confirmed as prostatic carcinoma.

prostatectomy. Transurethral ultrasound, if available, can also be used in the investigation of haemospermia.

Cystourethroscopy can be performed when the initial investigations have been negative (Pryor, 1985) and is especially important if the haemospermia is persistent or if there is associated haematuria. Using this method, 50% of cases recorded by Fletcher *et al.* (1981) had abnormal findings. Hyperaemia and oedema of the prostatic urethral mucosa are often seen. The mucosa may have a granular or polypoidal appearance (Pryor, 1985), particularly near the verumontanum, and these lesions occasionally occur with a long pedicle (Fig. 3). These papillary adenomata or adenomatous polyps are believed to be ectopic prostatic tissue (Stein *et al.*, 1980) which arises from a developmental error rather than signifying an initial step in the development of benign prostatic hyperplasia (Baroudy and O'Connell, 1984). Enlarged veins near the verumontanum or bladder neck or over an enlarged prostate may also be noticed. Abnormal veins seen coursing along the side of the verumontanum have been reported to cause massive haemospermia.

In one patient in our series, biopsy of this area showed haemangioma of the urethra (Fig. 4). These veins may not be visible during panendoscopy when the penis is flaccid. In another reported case (Cattolica, 1982) the patient engaged in coitus on Friday night and was subsequently admitted to



Fig. 3 Adenomatous polyp. (H and E $\times 86$).

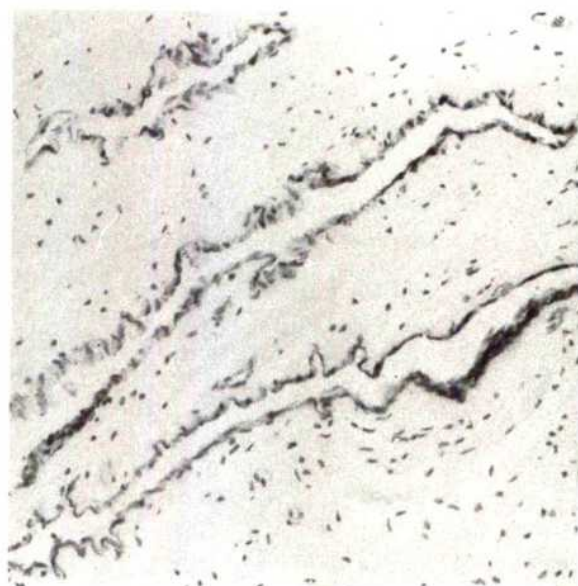


Fig. 4 Haemangioma of prostatic urethra. (Immunostaining for Factor VIII $\times 575$).

hospital after massive haemospermia and urinary retention. He was catheterised during the weekend and went back to work on the following Monday. These episodes went on for many weeks and the patient had several negative panendoscopic examinations. Finally the author found distended prostatic veins when the patient had an erection during the procedure and these were diathermised.

Carcinoma of the bladder or prostatic urethra can be found, but is a rare occurrence. In our series a 47-year-old man presented with haemospermia and haematuria. Biopsy of the prostatic urethra initially showed carcinoma *in situ* (Fig. 5) which within a few months progressed to an aggressive transitional cell carcinoma with metastases.

Urethroscopy occasionally reveals prostatic calculi or corpora amylacea beneath the prostatic mucosa (Pryor, 1985). The openings of the ejaculatory ducts can also be visualised during massage of the seminal vesicles and blood may be seen extruding from the orifices (Fletcher *et al.*, 1981). Urethral condylomata or warts can also be seen during this procedure.

Computed tomography and magnetic resonance imaging (MRI) are useful in selected cases, especially in patients with doubtful lesions on transrectal ultrasound. MRI scan is particularly useful in demonstrating seminal vesicular lesions (Fig. 6).

Vasography, as advised by Fletcher *et al.* (1981), now has a limited role with the increasing use of

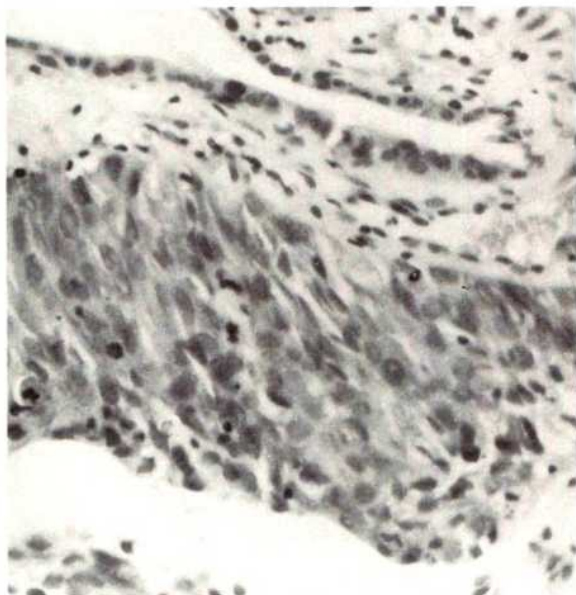


Fig. 5 Prostatic urethral biopsy showing carcinoma *in situ*. (H and E $\times 575$).

modern imaging techniques such as transrectal ultrasound. Vasotomy is invasive and may cause subsequent obstruction of the vas deferens. It should therefore be considered only when all of the preceding investigations have been negative and there is a palpable abnormality of the seminal vesicles.

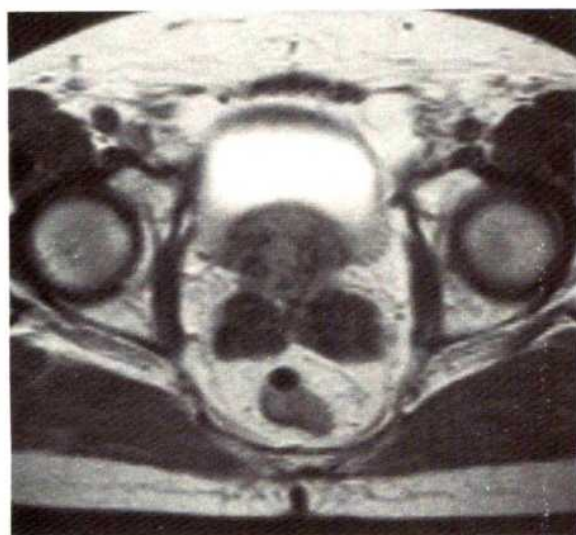


Fig. 6 Magnetic resonance imaging showing seminal vesicular dilatation.

Treatment

Patients presenting with haemospermia are frequently anxious and apprehensive. It is therefore important to spend time reassuring them that the symptom is very unlikely to herald any serious underlying pathology.

The treatment of haemospermia is based on the underlying pathology. Infection is treated with the appropriate antibiotic according to the sensitivity of the cultured organism. Only antibiotics known to be secreted in the prostatic fluid should be used. These include trimethoprim, erythromycin, ciprofloxacin and cephalosporins. When an infective cause is suspected and the culture is negative (as often occurs with *Chlamydia* or *Bacteroides*), treatment with a full course of one of the tetracyclines or metronidazole may be given.

Bleeding from the abnormal veins in the prostatic urethra can be fulgurised (Cattolica, 1982). Polyps, granulations or papillary adenomata, if seen, should be biopsied with cold cup biopsy forceps to rule out a malignancy (Stein *et al.*, 1980) and if necessary may also be diathermised (Baroudy and O'Connell, 1984). Considerable caution must be exercised because of the anatomical proximity of the external sphincter and the verumontanum (Baroudy and O'Connell, 1984). The rare utricular cyst is either aspirated transrectally under ultrasound guidance or, alternatively, the utricle can be dilated endoscopically and the cyst emptied by digital rectal massage (Van Poppel *et al.*, 1983).

Persistent haemospermia is troublesome and difficult to treat in the absence of significant positive findings. Huggins and McDonald (1945) confirmed the bleeding from the seminal vesicles by a 3-glass test and successfully treated the patients with a short course of ethinyl oestradiol in small doses. Yada (1963) tried corticotrophin and an anti-allergic substance called neominophagen C, but such measures would now seem unnecessary. Fuse *et al.* (1988) treated 7 such patients with bilateral seminal vesicular aspiration, under transrectal ultrasound examination, and injected a mixture containing an antibiotic, a coagulant, an oestrogen and hydrocortisone with complete success for 2 to 3 months.

Conclusion

It is now possible to identify the cause of haemospermia in most cases (Pryor, 1985). In younger patients (below 40 years of age) benign conditions are common and in these patients the extent of

management may be safely limited to history, general physical examination including digital rectal palpation, urine analysis and culture and, if necessary, antibiotic treatment. If the haemospermia persists, if the patient is over 40 years of age, or if haematuria (even microscopic) is present, the patient should be investigated (Hirah, 1989). This should include imaging with transrectal ultrasound before proceeding to more invasive and expensive procedures such as cystourethroscopy or vasography.

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Radiation Protection in Percutaneous Renal Surgery

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Summary—Two British centres have published the radiation doses received during percutaneous nephrolithotomy (PCNL). Their results were disparate. This study was performed to establish the likely exposure of the eyes and fingers of an experienced urological surgeon who creates the track into the kidney and also performs the endoscopic operation. In addition, some radioprotective gloves were evaluated. Provided that specific precautions, including a judicious use of screening, are taken, the current dose limits are unlikely to be exceeded. However, a 30% reduction in the dose limits is probable. Wearing routine radiation badges under a lead apron is an inadequate method of monitoring exposure: urologists should press for more active assistance from radiation protection officers in the monitoring of procedures in theatre and the use of ultrasound should be encouraged.

Radiation protection is an emotive subject and there is international debate on what constitutes a safe radiation dose.

In radiation protection the internationally agreed unit of radiation dose is the sievert (Sv). This unit takes into account the increased biological effectiveness of the more densely ionising radiations such as neutrons or alpha particles, which dissipate all of their energy superficially and may therefore cause maximum damage to the skin. Electrons, however, dissipate their energy in longer tracks and can penetrate deeper tissues. A dose of 1 μ Sv is equivalent to 20 minutes' air travel and 6 Sv is the dose likely to cause 90% mortality in exposed people. The urologist may be exposed to radiation during percutaneous nephrolithotomy both during the development of the track and following the endoscopic procedure to check clearance of stone. Whilst ultrasound guided PCNL has not proved popular thus far in the UK, it is used successfully elsewhere.

Two British centres have published data on the radiation doses received during PCNL. Their results were very different. This study was performed to establish what is the likely exposure for

an experienced urological surgeon who creates the track into the kidney and also performs the endoscopic operation.

Methods

In order to monitor the doses received during PCNL at St Bartholomew's Hospital and the Homerton Hospital, calibrated microchip TLD disks were worn on the index fingers of both hands, under standard latex surgical gloves and between the eyes. The disks were worn by an experienced surgeon during the creation of the track under X-ray control and during the endoscopic procedure. Doses were recorded using the overcouch Schimadzu equipment at St Bartholomew's Hospital and using the Siemens undercouch C-arm equipment at the Homerton Hospital.

In addition, the X-ray attenuation of some newly available radioprotective surgical gloves (Porges) was evaluated in the Department of Radiation Biology. The specific claims made for the X-ray attenuation of the gloves were tested using dosimetry with a tissue equivalent ionisation chamber in an irradiation unit. These observations were compared with the attenuation obtained from standard latex surgical gloves. The gloves were worn during percutaneous surgery and their comfort was noted.

Results

The mean screening time was 2.0 min (range 0.3–2.8). The results of the microchip recordings are summarised in Tables 1 to 3. The mean doses received by the forehead, right index finger and left index finger were 0.12, 0.145 and 0.14 mSv respectively. Lower doses were received by the finger tips and forehead using the undercouch apparatus compared with the overcouch unit.

The attenuation of the gloves (Table 4) broadly matched the manufacturer's claims—with a 63% attenuation at 80 kVp (common voltage in clinical use). This compares with the 3% attenuation obtained by using 5 thicknesses of Regent Dispo gloves with X-rays at 80 kVp. The radioprotective gloves were comfortable in clinical use.

Discussion

Two British centres have published data on this subject. Rao *et al.* (1987) recorded doses received by the finger, wrist and forehead of the urologist and by the finger, wrist, chest and forehead of the radiologist during PCNL at the University Hospital of South Manchester; the radiologist developed the track and the urologist performed the endoscopic procedure. To allow comparison, the doses from the separate parts of the procedure have been added. Rao *et al.* (1987) documented a mean total radiation dose to the hands of 5.2 mSv, to the fingers of 7.5 mSv and to the eyes of 1.6 mSv with a mean screening time of 21.9 min. Law *et al.* (1989) and Inglis *et al.* (1989) reported from Edinburgh. Recordings were made, as in the current study, from a surgeon who made the track and performed

Table 1 Operator Doses during Percutaneous Renal Surgery (arithmetic means with the number of observations in parentheses)

	Doses received (mSv $\pm$ SD)
Forehead	0.12 $\pm$ 0.12 (n=14)
Right index finger	0.145 $\pm$ 0.12 (n=14)
Left index finger	0.14 $\pm$ 0.13 (n=13)

Table 2 Overcouch Data (arithmetic means with the number of observations in parentheses)

	Doses received (mSv $\pm$ SD)
Forehead	0.19 $\pm$ 0.12 (n=8)
Right index finger	0.21 $\pm$ 0.12 (n=8)
Left index finger	0.23 $\pm$ 0.12 (n=7)

Table 3 C-arm Data (arithmetic means with the number of observations in parentheses)

	Doses received (mSv $\pm$ SD)
Forehead	0.03 $\pm$ 0.015 (n=6)
Right index finger	0.05 $\pm$ 0.04 (n=6)
Left index finger	0.035 $\pm$ 0.02 (n=6)

Table 4 Attenuation of Radioprotective Gloves (Porges)

kV	40	60	80	100
Dose in air (cGy/min)	200	811	1377	1926
With gloves (cGy/min)	37	239	512	864
% Attenuation	82	71	63	55

the endoscopic procedure. Monitors were worn on the fingers and over the thyroid. In the latter study, the mean dose to the fingers was 0.34 mSv per patient, whereas the dose to the thyroid was less than 0.035 mSv per patient: the dose to the thyroid was cited as being equivalent to the eye dose, although this is probably not so when a surgeon is leaning over the patient.

The finger doses recorded by Law *et al.* (1989) and Inglis *et al.* (1989) are of the same order of magnitude as those in the current study, whereas the finger and eye doses recorded by Rao *et al.* (1987) are considerably larger.

Are these doses safe and how can they be interpreted? The current answer, for the United Kingdom, is found in the ionising radiations regulations of H.M.S.O (1985). This is a legally binding Government publication documenting safe dose limits for employees. The regulations stipulate annual radiation dose equivalent limits for the skin and the eyes. For employees aged 18 years and over, the annual dose limit for the lens of the eye is 150 mSv and for a finger it is 500 mSv.

In the United Kingdom, the National Radiation Protection Board (NRPB) is usually guided by the International Commission on Radiation Protection (ICRP). A cut in the ICRP dose limits of 30% is likely within the next year (International Commission on Radiation Protection, 1990).

It is seen from the data of Rao *et al.* (1987) that the dose limits could be exceeded in a stone centre using equivalently long screening times. Law *et al.* (1989) and Inglis *et al.* (1989) documented a mean screening time of 4.4 min, compared with 2.0 min in the current study. It would appear that the current dose limits are unlikely to be exceeded in these centres but the probable future changes in the

ionising radiations regulations leave no grounds for complacency.

With the obligation for training of persons directing medical exposures (H.M.S.O., 1988), an understanding of these specific risks is important. How can the risks be decreased? The principle referred to by experts in radiation protection is the ALARA principle—as low as reasonably achievable. The reasonably achievable precautions in theatre are probably widely appreciated: the use of an undercouch screening unit, carbon fibre in the operating table, lead aprons, lead glass viewing screens and minimising the number of staff exposed to X-rays.

However, there are some reasonably achievable precautions for the operator which are not always taken: minimising the screening time, fully coning down X-rays and the wearing of radioprotective gloves, a thyroid collar and radioprotective spectacles. Whilst radioprotective surgical gloves are more expensive than latex gloves, the former can be re-sterilised using ethylene oxide.

There are 2 technical (and sometimes underemphasised) points which assist in keeping screening time to a minimum: the surgeon should control the foot pedal of the image intensifier and the image intensifier should have a memory capacity.

Wearing routine radiation badges under a lead apron is an inadequate method of monitoring exposure. Perhaps urologists should press for more active assistance from radiation protection officers in the monitoring of procedures in theatre. The dispensing, collection and measurement of TLD badges is not enough. The use of ultrasound should be encouraged.

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Recurrent Infection Stones with Apparently Negative Cultures. The Case for Blind Antibacterial Treatment

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Summary—Infection stones in the urinary tract are always associated with infection with a urease-producing, urea-splitting organism. The most common of these organisms are easy to culture and identify and can be treated early either with an appropriate antibiotic or with an anti-urease agent. *Ureaplasma urealyticum* and *Corynebacterium urealyticum* are urease-producing organisms which are difficult to grow; their presence and effects frequently go undetected and untreated. Other organisms, as yet unknown, may also be involved in the same process.

We report the first series of 8 patients with recurrent infection-type stones likely to have been caused by a "hard to grow" organism. Five patients never had a positive culture; in 2 patients 1 of 10 urine cultures grew a coagulase-negative *Staphylococcus* and in 1 patient the same organism was grown from a stone but never in the urine.

The clinical course of all of these patients was significantly improved after blind treatment with antibiotics and in one case with an anti-urease agent.

The importance of urea-splitting organisms in the production of urinary stones was recognised and demonstrated in the experimental animal more than 40 years ago (Chute and Suby, 1940).

In the western world, between 10 and 20% of all upper urinary calculi appear to be infection stones (Lerner *et al.*, 1989).

Infection stones are composed of struvite (magnesium ammonium phosphate) (MAP) and carbonate-apatite (calcium phosphate carbonate). The enzyme urease breaks down urea into ammonia and carbon dioxide, thereby increasing the pH of the urine (Griffith *et al.*, 1976).

Urease is produced by a number of organisms, the most important of which are of the genus *Proteus*, but also by some *Pseudomonas*, *Klebsiellas* and *Staphylococci*. Most of these organisms can be readily cultured and identified in samples of urine and of crushed stone.

Ureaplasma urealyticum is a urease-producing

organism commonly found in the lower urinary tract of sexually active men and in women of child-bearing age but not normally in the upper urinary tract. It is an organism which is difficult to identify since it does not grow in standard urine culture media (Pettersson *et al.*, 1983; Hedelin *et al.*, 1984). It is associated with non-specific urethritis (Bowie *et al.*, 1977b), stone formation in the experimental animal (Grenabo *et al.*, 1985), stones in Skene's gland (Gellman and Dershewitz, 1986) and infection stones in the upper and lower urinary tract in the human (Grenabo *et al.*, 1988).

Ureaplasma urealyticum has been identified as the sole organism in the pelvic urine and in the stones of some infection stone-forming patients (Hedelin *et al.*, 1984; Minetti *et al.*, 1984).

It has been cultured from the stones and from the pelvic urine of a patient with recurrent "infection stones" when no micro-organism could be found in conventional urine cultures (Grenabo *et al.*, 1986). The elimination of this infection has also been associated with either cure or marked improvement in some patients with recurrent infection stones (Grenabo *et al.*, 1986; Janitzky *et al.*, 1989).

Corynebacterium urealyticum (group D2) is another "hard to grow" urease-producing, urea-splitting organism which is rarely identified. It has been found to be the cause of a case of alkaline-encrusted cystitis (Soriano *et al.*, 1985) and to be associated with stone formation *in vitro* and *in vivo*.

We report the first series of 8 patients with recurrent infection-type stones in which no organisms could be identified by conventional cultures or in which a suspected pathogen was identified and treated but the stones recurred with subsequent negative cultures. In some of these patients, specific cultures for *Ureaplasma urealyticum* in the urine and in the stone were attempted but were negative. Infection with a "hard to grow" organism was assumed and the symptoms markedly improved in all patients after blind treatment with antibiotics or with the anti-urease agent propionhydroxamic acid (PHA).

Patients and Methods

All of the patients were attending the metabolic stone clinic of St Peter's Hospitals and had been thoroughly investigated for the usual metabolic causes of urinary stones without any abnormality being found.

The diagnosis of infection as the cause of the stone or gravel was based on the finding of the characteristic composition of magnesium ammonium phosphate either with or without added calcium phosphate. Stones and gravel were quantitatively analysed by thermogravimetric analysis (Rose and Woodfine, 1976) supplemented by wet chemistry (Westbury, 1974). Urine pH was measured using a pH meter upon freshly passed urine maintained at 37°C. Fresh urine was centrifuged at 37°C and the deposit was examined microscopically while maintaining the same temperature.

Case Reports

All patients were male. The age range at presentation was 25 to 63 years (mean 42.1).

Case 1. A.P. First stone passed in 1966. Open pyelolithotomy in 1978 (stone analysis: calcium phosphate with 22% MAP). Bilateral staghorn calculi were found in 1987 and he was transferred to our care. The stones were removed by bilateral open surgery (stone analysis: calcium phosphate with 52% MAP). Stone culture was negative but was not specifically carried out for *Ureaplasma*. Repeated urine cultures showed pyuria but were sterile.

Four and 9 months after the second operation he had 2 positive urine cultures which grew coagulase-negative *Staphylococci* with marked pyuria (Table 1) and he was treated with short courses of antibiotics (Table 2). Stone formation continued on review 18 months later. A total of 23 urine cultures were negative but 15 showed pyuria. Specific *Ureaplasma* urine culture was negative (10/9/87). He has now been on PHA + Furadantin for 2 years with no further stone growth.

Case 2. M.B. Patient with medullary sponge kidneys who passed numerous stones and gravel for 18 years, and bladder calculi which required removal by open surgery. Bladder stones recurred 4 years later. Analysis: 9% MAP. The first 6 urine cultures were negative but all showed marked pyuria. He was given a short course of gentamicin after the seventh culture grew coagulase-negative *Staphylococci*. Three further cultures were negative but still showed pyuria, although in the last one this was considerably reduced (Table 1). Urine was not specifically cultured for *Ureaplasma*. He has had no further stone growth for 1 year on low dose doxycycline.

Case 3. B.M. Recurrent gravel and "chalky urine" once a week for 3 years. Gravel analysis: 58% MAP. Four urine cultures were negative; only 1 had "few" white cells (Table 1). Urine was not specifically cultured for *Ureaplasma*. He was given a 3-month course of Septrin and has now been asymptomatic for 2 years.

Case 4. A.G. Experienced many events of loin pain, ureteric stones and chalky urine for more than 10 years. Stone analysis: 12% MAP. Five urine cultures were negative with few white cells and 3 were negative with no white cells (Table 1). Urine was not specifically cultured for *Ureaplasma*. He then received various antibiotics, all of which were stopped owing to side effects. He is now much improved on low dose Ciprofloxacin for 18 months, although he still passes "a few bits of grit" every 4 to 8 weeks.

Case 5. R.F. Renal colic and ureteric stone 7 times in 4 years. Stone analysis: 5% and 8% MAP. Two urine cultures were negative with no white cells (Table 1); 2 specific *Ureaplasma* urine cultures were negative. Culture of gravel passed 3 months after starting treatment grew urease-positive, coagulase-negative *Staphylococci*. He continued on Septrin for a further 3 months and showed no more symptoms after a 1-year follow-up.

Case 6. P.I. Passed over 50 stones in 30 years. Latest analyses 7% and 14% MAP. Three urine cultures were negative, 1 of which showed a few white cells (Table 1). Urine was not specifically cultured for *Ureaplasma*. He underwent 3 years of treatment with doxycycline and Ciprofloxacin at sub-optimal doses owing to side effects. There is now some improvement on Furadantin, although he is still passing a small stone approximately every 6 months.

Table 1 Cultures of Voided Urine

No.	Patient	Date	Growth	White cells
1	AP	12/67	few colif	5
		12/77	neg	nil
		2/78	neg	50
		8/78	neg	nil
		2/87	neg	many
		2/87	neg	80
		2/87	neg	12
		2/87	neg	nil (post op)
		3/87	neg	nil
		3/87	neg	160
		4/87	neg	?
		4/87	neg	120
		4/87	neg	nil
		4/87	neg	40
		4/87	neg	40
		5/87	neg	nil
		5/87	neg	?
		5/87	neg	?
		5/87	neg	many
		6/87	coag-ve staph	210
		7/87	mixed	many
		11/87	mixed	?
		1/88	coag-ve staph	120
		3/88	neg	100
		6/88	neg	60
		6/89	neg	80
2	MB	5/88	neg	100
		7/88	neg	many
		7/88	neg	many
		7/88	neg	many
		7/88	neg	many
		8/88	neg	many
		10/89	coag-ve staph	160
		11/89	neg	many
		12/89	neg	many
3	BM	4/90	mixed	16
		5/87	neg	4
		3/88	neg	nil
		3/88	neg	nil
4	AG	6/88	neg	nil
		3/83	neg	nil
		3/83	neg	nil
		9/86	neg	20
		2/87	neg	nil
		9/87	neg	4
		9/88	neg	12
		6/89	neg	4
5	RF	10/89	neg	12
		7/87	neg	nil
6	PI	8/87	neg	nil
		6/89	neg	nil
		9/89	neg	16
7	KF	10/87	neg	nil
		11/87	neg	16
		10/88	neg	nil
		10/89	neg	24
		4/90	neg	?
8	MC	5/88	neg	nil
		6/88	neg	16
		11/88	neg	nil
		11/88	neg	nil
		6/90	neg	4

Case 7. K.F. Recurrent ureteric stones for 15 years (passed more than 50). Several stones in kidneys. Stone analyses 21%, 12%, 9% MAP. Five urine cultures were negative, 2 of which had a few white cells (Table 2). Specific *Ureaplasma* urine culture was negative. Much improved on doxycycline 100 mg daily but still passing stones occasionally.

Case 8. M.C. Bilateral renal calculi presenting with acute colic. History of recurrent urinary infections, arthritis, headaches and uveitis. Percutaneous removal + lithotripsy. Stone analysis 26% MAP. Five urine cultures were negative; 2 had a few white cells (Table 1). Urine was not specifically cultured for *Ureaplasma*. He underwent 6 weeks' treatment with doxycycline and showed great improvement in all symptoms. Had recurrent colic with stone passage when reviewed 18 months later and being off antibiotics.

Summary of clinical courses

All patients showed marked symptomatic improvement after the introduction of treatment with antibiotics or the anti-urease agent PHA. Patients 3 and 5 were apparently cured. Patients 1 and 2 are stable and not forming stones. Patients 4, 6 and 7 are improved and stable, although still passing some stones. Patient 8 received only 6 weeks of treatment, with great improvement, but had further stone passage 18 months after stopping treatment; review of the X-rays showed that he had passed one remaining old stone but was also making and passing new stones.

Stone analysis

Stone analysis in all patients revealed the presence of MAP and calcium phosphate in most of the stones (Table 2).

In patients 6 and 7 some stones contained calcium oxalate in various proportions. The remaining patients had stones made of MAP and calcium phosphate which never contained calcium oxalate. In some cases there was also a small amount of matrix, but this was never more than 5% of the stone weight. The elements calcium, magnesium, oxalate and phosphate in the stones were also measured and are shown in Table 2.

Urine analysis

Several samples of fresh urine were analysed microscopically for crystals as described above, but the results did not provide any additional diagnostic or prognostic information.

The pH of the fresh urine was also measured and the mean pH for each patient was obtained (Table

Table 2 Stone Analysis, Antibiotic Treatment and Mean Urinary pH

No.	Patient	Date	Antib.	MAP (%)	Ca. PO ₄ (%)	CaOx (%)	Ca ⁺⁺ (%)	Mg ⁺⁺ (%)	Ox ⁻⁻⁻ (%)	Phos. (%)	pH
1	AP	2/78		22	rest	0	25.3	2	0	11.8	6.71
		4/87		52	rest	0	21.6	4.9	0	12.3	
		6/87	Amp for 2/52								
		9/87	Sep for 3/12								
		1/88	Fluclox by GP								
		9/88	Furad + PHA								
		6/90	On same treatment								
2	MB	8/88		9	74	0	25.6	0.8	0	14.6	6.90
		10/89	Gent for 3 days								
		12/89	Dox								
		4/90	On same treatment								
3	BM	11/87		58	23	0	10.5	5.4	0	8.6	5.67
		3/88	Sep	9	75	0					
		7/88	stop								
4	AG	1/86		10	rest	0	20.1	0.9	0	13.0	6.65
		2/87	Sep	19	rest	0	16.1	1.8	0	10.9	
		9/87	stop								
		10/87	Sep	12	68	0	26.4	1.2	0	15.6	
		3/88	Dox. rash								
		6/88	Trim: rash								
		12/88	Cephadrine: no effect								
		3/89	Cipr	7	79	0	30.7	0.7	0	16.6	
5	RF	5/90	On same treatment								7.38
		7/87		8	+++	0	28.0	0.7	0	15.0	
		8/87	Sep	5	73	0	19.8	0.5	0	11.8	
		3/88	stop								
6	PI	8/87	Sep	36	60	0	29.6	3.4	0	14.7	6.53
		8/87		26	64	0	31.6	2.4	0	14.2	
		8/87		4	32	58	27.9	0.4	31	7.1	
		8/87				89			48		
		12/87	Dox								
		2/88		5	rest	49	32.2	0.5	25	11.9	
		9/89	stop			98			53		
7	KF	11/87	Dox	12	67	16	31.3	1.1	9	15.1	6.97
		1/88		3	36	58	29.9	0.3	31	8.5	
		4/88		10	71	0	27.8	1.0	0	15.8	
		10/88	Sep	8	75	0	31.6	0.8	0	15.6	
		4/89	Dox	11	89	0	33.1	1.1	0	18.2	
		4/89		13	60	0	24.1	1.3	0	13.4	
		10/89	Dox	11	67	18	27.4	1.1	10	15.8	
		1/90	stop								
		8/90		9	62	16					
8	MC	5/88		26	55	0	21.5	2.4	0	14.5	7.83
		11/88	Dox								
		12/88	stopped after 5/52								
		1/89	Symptoms recurred 3 months after stopping								

Antib = Antibiotic; Phos = Phosphate; Amp = Ampicillin; Sep = Septrin; Fluclox = Flucloxacillin; Furad = Furadantin; Gent = Gentamicin; Dox = Doxycycline; Trim = Trimethoprim; Cipr = Ciprofloxacin.

N.B. In some cases there was also a small amount of matrix which never exceeded 5%. pH mean of means: pH 6.83

2). Although there was a trend towards alkalinity, this was only slight (see below).

Urine cultures

Only in patients 1 and 2 were urease-producing

organisms ever grown in the urine (Table 1). In patient 5 a urease-positive, coagulase-negative *Staphylococcus* was grown from the gravel but not from the urine.

Some of the patients had persistent and signifi-

cant pyuria. However, this was not the case in patients 3 and 5, who produced the most dramatic results when treated with antibiotics (Table 1).

Discussion

Recurrent infection stones due to "hard to grow" organisms is a relatively rare condition. There are no previously published series and a single case with a 6-month follow-up has been reported (Grenabo *et al.*, 1986). Hedelin *et al.* (1984) reported the presence of *Ureaplasma urealyticum* in a series of 7 stone patients but did not report on the follow-up, and Janitzky *et al.* (1989) reported a series of 29 patients with recurrent/residual infection stones with persistent urinary infection.

This is the first reported series of patients with recurrent infection stones presumably due to "hard to grow" organisms which were specifically treated and with a follow-up of 8 to 36 months.

All the patients had stones containing MAP and so they must have had an infection with a urea-splitting organism. Since MAP is the only form in which magnesium is present in urinary stones, we found that the amount of this element was always proportional to the amount of MAP (Table 2). Magnesium in urinary stones could, therefore, also have been taken as an indication of infection with a urea-splitting organism. However, it was not possible to culture a responsible organism in most of our patients. In the 3 patients in whom a coagulase-negative *Staphylococcus* was found in the urine or stone, several other urine cultures from each patient were negative, although pyuria was occasionally found. Since these patients continued to form stones with MAP, it has to be assumed that a urea-splitting organism was present but could not be identified with our methods. It has been shown that *Ureaplasma urealyticum* may be the responsible organism in such cases and antibiotic treatment can produce a cure (Grenabo *et al.*, 1986). All of our patients were apparently either cured or had significantly reduced stone formation when treated blindly with antibiotics or with an anti-urease agent.

Ureaplasma urealyticum is usually sensitive to tetracyclines and erythromycin (Braun *et al.*, 1970). Doxycycline was found to be the most effective antibiotic; in some cases other antibiotics had to be used because of bacterial resistance or side effects. *Ureaplasma urealyticum* is present in the urethra of most normal sexually active men and in women of child-bearing age. When re-infection occurs, cross-infection should be suspected and

requires the investigation and treatment of the patient's sexual partner.

Corynebacterium urealyticum has been shown to be more resistant to antibiotics (Santamaria *et al.*, 1985). In these cases, and in the absence of a positive culture, the "trial and error" approach to the use of various antibiotics or an anti-urease agent may be indicated.

Antibiotics may be less effective or may become inactive in the alkaline medium created by the urea-splitting process. This appears to be a further indication for the use of an anti-urease agent. PHA is an anti-urease agent which has been shown to be effective in the treatment of this type of patient and has few side effects, although experience so far is limited (Martelli *et al.*, 1986; Soriano *et al.*, 1987). The addition of PHA was successful in one of our patients.

Stone recurrence may also be related to an underlying metabolic disorder. Although no such disorder could be confirmed in any of our patients, the presence of stones containing calcium oxalate in 2 cases suggests a combination of infection and metabolic abnormality. Patient 6 had excess cystine and lysine in his urine ("semi-cystinuria") (Harris and Warren, 1953) but never passed any cystine stones, as often happens in these patients. Furthermore, some of his very early stones were reported to be mainly of calcium oxalate; prior to our treatment he used to take vitamin B6. He could have had a concealed mild metabolic hyperoxaluria (Gill and Rose, 1986; Rose, 1988). Thereafter he appears to have acquired an infection with a urea-splitting organism as he started producing stones with MAP. After treatment with antibiotics, the metabolic stone-forming disorder again became evident as his stones were again mainly composed of calcium oxalate.

In patient 7 the presence of calcium oxalate in the first and last stones points towards the possibility of a combination of metabolic abnormality and infection. Treatment with antibiotics produced a great improvement but not a complete cure. It should be remembered that metabolic stones can become infected and infection stones may act as a nidus for later calcium oxalate deposition.

The duration of antibacterial treatment required in these patients is difficult to define. Unfortunately, the disappearance of pyuria cannot be taken as a guide since 75% of our patients had very few or no white cells in the urine initially (Table 1). It appears from our experience that a long course of a low dose treatment may be necessary in most cases and that vigilance is necessary after stopping treatment in

case of recurrence. Patient 8 is a classic example of recurrence after a short course of antibiotic treatment. He is likely to have been reinfected by his sexual partner, who should probably have been treated as well.

The urea-splitting process produces an alkaline urine. In our patients the mean of the means pH of the fresh urine was 6.83 (Table 2). This is slightly higher than the 6.3 to 6.5 found in other stone patients (Rose, 1991). One must wonder whether MAP stone formation could occur under these conditions. We propose as the explanation that the infection is often localised to a small area, perhaps a single calix, and that the alkaline conditions are only local; the rest of the urinary system, being free from infection, would continue producing a more acid urine and the pH of the resulting pool would be near normal. The "localised infection" may also be the explanation for the absence of a significant number of white cells in the pooled urine of most of our patients, although this contradicts previous conventional understanding of urinary infection.

In our experience, the presence of MAP-containing stones is a reliable indication of infection. We cannot find any evidence that MAP in stones can be produced in humans in any other way. The absence of pyuria and a normal urinary pH are irrelevant in these cases. In the presence of recurrent symptoms due to MAP-containing stones, appropriate antibacterial treatment is indicated.

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Prevalence of Upper Urinary Tract Stone Disease in a Rural Community of North-eastern Thailand

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Summary—A survey was conducted of upper urinary tract stone (UUTS) disease in an administrative subdivision of Khon Kaen Province in Thailand. Initial case screening was done by direct contact with the village health volunteers and village health communicators. A positive patient was defined as one who had had surgery for UUTS, previously been diagnosed by physicians, or had a history of stone passage. Those who belonged to the latter 2 categories were confirmed radiologically. The prevalence of UUTS was 3.76/1000. The male/female ratio was 2:1. The average age was 50 ± 13 years (range 8–71). Common associated symptoms were back pain, abdominal pain, painful urination, stone passage and blood-stained urine; 75% of the patients were from a poor socio-economic class. The data suggest that UUTS is common in north-eastern Thailand. Although this is an approximate and, perhaps, an underestimated prevalence, the present method is cost-effective, efficient and appropriate for conducting community surveys in developing nations.

Urinary tract stone disease is said to be common in rural north-eastern Thailand. A previous survey showed that the prevalence of lower urinary tract stone disease in this area was as high as 38/1000 (Halstead and Vallyasevi, 1967). Upper urinary tract stone disease was also believed to be common in this part of the country. Recent studies of hospital admissions show a sharp rise in the incidence of UUTS to 50 to 85% of patients admitted for urinary stone surgery (Raiyawa *et al.*, 1985; Chatudompan, 1987), but the true prevalence in the rural community remains unknown. We present a survey of the prevalence of UUTS in a rural community in north-eastern Thailand.

Patients and Methods

The study was conducted in the administrative subdivision of Baan Fang (area 153.5 square miles, population 48,400) in the suburb of Khon Kaen municipal area, north-eastern Thailand. It consists

of 7 village groups, 54 villages and 8,292 households. The population comprised mostly farmers or peasants. Initial screening of suspected cases of UUTS was made by village health volunteers (VHV) and village health communicators (VHC). These were native residents of each village and were responsible for providing primary health care to the community. They reported by mail the suspected cases to one of the authors (P.S.). A home visit and direct interview was made by one of the 2 investigators (P.S. and K.C.) in all suspected cases. Criteria for inclusion were a history of passing stone, a previous diagnosis of UUTS by a physician, or previous UUTS surgery. For those who met the first 2 criteria, radiological confirmation was required before inclusion. Since the number of households within the responsibility of each VHV and VHC was limited and well defined, this method of case detection ensured adequate coverage of the target population. General clinical information and socio-economic status were evaluated. Accurate individual income was difficult to estimate because of differences in the number of dependent members in the family, the cost of land-

leasing for plantation, the price of cultivated crops and income from part-time jobs. It is more valid to define the socio-economic status of each subject based on the annual income per household. The survey was carried out between January and May 1989.

Results

A total of 182 patients were eligible for the study (Table 1). They were evenly distributed between the 3 criteria, *i.e.* about one-third each had a history of passing stone, previous diagnosis of UUTS or previous stone surgery. The prevalence was 3.76/1000 population. The mean age ($\pm$ SD) was 50 ± 13 years. The peak of age incidence was in the fifth decade (15/1000 population) (Fig.). The disease

was male-preponderant in all age groups, with an overall male/female ratio of 2:1.

One-third of the patients had multiple stones and one-fifth were bilaterally involved (Table 2). For those in whom the site of the stones could be demonstrated radiographically, renal, pelvicaliceal and staghorn calculi accounted for nearly 75%. Six patients (3%) had concomitant bladder stone disease.

Common symptoms were back pain with or without absence from work, ureteric colic, blood-stained urine, spontaneous stone passage and painful urination. Most cases had more than one symptom at the time of interview (Table 3). Since the daily activities of our subjects were labour-intensive, it was difficult to ascertain whether the back pain was caused by physical labour or by UUTS *per se*.

A family history of urinary stone was present in 88 cases (48%) (Table 4). One or 2 members of the family were usually affected, the brother/sister relationship being the most frequent.

The annual income per household averaged US\$

Table 1 Prevalence of Upper Urinary Tract Stone Disease

No. of patients	182
History of stone passage	54 (30%)
Previous diagnosis	59 (32%)
Previous surgery	69 (38%)
Prevalence per 1000 population	3.76
Age $\pm$ SD (range) (years)	50 ± 13 (9-83)
Male/female	123/59 (2:1)

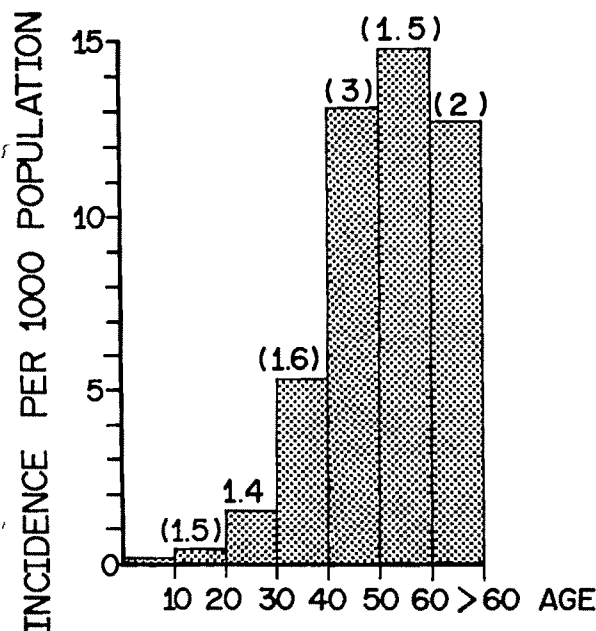


Fig. Incidence of upper urinary tract stone disease in north-eastern Thailand by age. The numbers in parentheses represent the male/female ratio for each age interval.

Table 2 Distribution of Stones According to Number and Location of the Stone

	(%)
No. of stones/patient	
1	116 (64)
2	28 (15)
3	9 (5)
> 3	29 (10)
Side	
Left	65 (36)
Right	82 (45)
Bilateral	35 (19)
Sites	
Renal	109 (60)
Staghorn	21 (12)
Caliceal	36 (20)
Ureteric	26 (14)
Undetermined*	38 (21)
Associated bladder stone	6 (3)

* Mostly in patients with a history of previous stone surgery.

Table 3 Signs and Symptoms

	(%)
Back pain with absence from work	108 (59)
Back pain without absence from work	154 (85)
Abdominal colic	113 (62)
Painful urination	115 (63)
Stone passage	108 (59)
Blood-stained urine	103 (57)

Table 4 Familial Data

No. of patients with family history of UUTS	88 (100%)
No. of family members with concomitant UUTS	
1	61 (69)
2	23 (26)
3	2 (2)
> 3	2 (2)
Relation of affected members to study group	
Father/mother	10 (11) / 4 (5)
Brother/sister	42 (48) / 11 (13)
Son/daughter	15 (17) / 6 (7)
Cousin	1 (1)

Table 5 Annual Income per Household (AIPH) of each subject

AIPH (US\$)	No of patients (%)
No income	3 (2)
1-400	68 (37)
401-800	51 (28)
801-1200	27 (15)
> 1200	33 (18)
Average AIPH ($\pm$ SD)	US\$ 802 $\pm$ 760

802 $\pm$ 760 (Table 5). With a *per capita* gross national product of Thai citizens in 1988 of US\$ 1065 (Bank of Thailand, 1990), 75% of our patients had a below-average income. Their individual income may have been less, since our data were expressed as income per household.

Community surveys of UUTS in the English literature between 1959 and 1988 were reviewed. The methods of survey differed considerably (questionnaire mailing, review of medical records, direct interview and random selection), as did the population base studied (all ages and both sexes, adult only, male only, *etc*), ethnic groups (gypsies only) and the inclusion criteria (variable clinical symptoms, abdominal X-rays, history of previous diagnosis by a physician). The prevalence varied from 11.5/1000 population among Spanish gypsies to 137/1000 in middle-aged Swedish males. The prevalence of UUTS in the present report was lower than that reported elsewhere.

Discussion

The prevalence of UUTS in this series was low compared with previous studies (Table 6) and the true prevalence in this community may be higher. Those who were symptom-free, or were sympto-

Table 6 Community Surveys for Prevalence of Upper Urinary Tract Stone

Surveys	Population base	Methods of study	Prevalence per 1000 population	Reference
Rochester, USA 1950-74	All 39,763	MR: C/DU/SP + (Atypical C + AXR)	16.9	Johnson <i>et al.</i> (1979)
Central Israel 1957-58	All 30,292	DI: C/SP/PS/AXR	11.8	Frank <i>et al.</i> (1959)
Northern California, USA 1964-72	Adults, > 15 years 175,000	Q: PDP	25.2	Hiatt <i>et al.</i> (1982)
Uppsala, Sweden 1970-73	Male, 45-50 years 2322	Q: C, + SP/PS/AXR/ PDP	137	Ljunghall <i>et al.</i> (1975)
Germany 1979	Adults, > 18 years 10,130	NA	40	Vahlensieck <i>et al.</i> (1982)
Granada and Almeria, Spain 1982	Gypsies, all 16,492	DI: SP/PS/AXR/PDP	11.5	Ramirez <i>et al.</i> (1984)
United Kingdom 1987	Adults, 19-80 years 3386	RS + DI: AXR	35.9	Scott (1987)
Khon Kaen, Thailand	All	Q + DI: SP + AXR PDP + AXR/PS	3.76	Sriboonlue <i>et al.</i> (1992)

AXR = abdominal X-rays. C = ureteric colic. CS = clinical symptoms of urinary stone. DU = dysuria. DI = direct interview. MR = medical record. NA = not available. PDP = previously diagnosed by a physician. Q = questionnaire. PS = previous stone surgery. RS = random selection. SP = spontaneous passage of urinary stone.

matic but failed to gain access to the health service system and thus did not receive proper care, or were reluctant to report to the VHVs and VHCs upon survey, might have been overlooked. A short period of survey, the educational background of the population and the extent of secondary and tertiary health service coverage in the community might also have contributed to the low prevalence. Nevertheless, what we are proposing is an investigative method that might be appropriate for developing countries where human and financial resources are limited. We did not use abdominal X-rays as the gold standard for case detection, as previously described by Scott (1987). It would have given us more accurate data, but at a very high cost. We calculated that it would have cost approximately US\$ 170,000 and required more than 3000 working days to take abdominal films of the whole population of Amphur Baan Fang. This is not economically feasible. We did not use hospital or insurance health records for analysis (Johnson *et al.*, 1979; Hiatt *et al.*, 1982). This is because the coverage of health insurance and secondary and tertiary health service in rural areas of the country was inadequate. Instead, we adopted a more practical approach. The laborious workload on initial screening for suspected cases of UUTS was integrated into that of the primary health personnel who already existed in the rural communities. The positive cases were then identified and subsequently interviewed by the authors. This method was convenient, affordable and efficient. The project cost only US\$ 2,000 and was completed in less than 200 working days.

Although the accuracy of the prevalence we obtained is open to question, it is high enough to support the proposal that UUTS is an important health problem in north-eastern Thai communities. Were the results generalised to the whole Khon Kaen province (population 1.7 million), 5400 people would be affected by UUTS.

The male preponderance and the peak of age incidence in the fifth decade are in accord with findings reported elsewhere (Robertson *et al.*, 1980; Schneider, 1985). Although associated UUTS disease in related family members was frequently seen in this study, we could not demonstrate a well defined pattern of genetic inheritance (Trinchieri *et al.*, 1988). Since the affected patients shared the same environmental background, pathogenetic factors related to common external factors cannot be excluded.

It is interesting that most of our patients had a low socio-economic status. In some reports, agriculturalists were claimed to suffer least from UUTS

(Mates, 1969; Scott, 1987). It may be that the pathogenesis of UUTS in north-eastern Thailand is different from that in developed countries. Differences in environmental background might be a contributory factor. North-eastern Thailand lies in a tropical zone but the land is quite arid and dry. In summer, which lasts for 3 to 4 months, precipitation is negligible. Since artesian wells and tap water are scarce or not available, the villagers have to drink untreated well water. This may contain a substantial amount of contaminants that can contribute to urinary stone formation. In addition, differences in dietary intake might also play a role. A recent survey among healthy rural north-eastern Thais showed that their daily dietary protein and potassium intake was as low as 40 to 50 g and 15 to 30 mmol respectively (Puwasien *et al.*, unpublished data). Low urinary excretion of potassium and citrate, low serum potassium and a correlation between urinary excretion of potassium and citrate were observed in UUTS patients from north-eastern Thailand (Sriboonlue *et al.*, 1991). An increment in serum and urinary potassium after oral potassium chloride supplementation in these UUTS cases indirectly supports the hypothesis of low dietary intake of nutrients and certain minerals among the UUTS population.

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Renal Cortical Scarring in Acute Pyelonephritis

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Summary—A series of 14 patients with acute pyelonephritis was evaluated for the formation of renal scarring by serial computed tomography (CT) and intravenous urography. Although the urography results were normal, CT showed renal parenchymal atrophy (cortical scarring) in 6 patients. Cortical scarring was observed to occur after 61 to 187 days, and it was slower to develop in the patients with recurrent fever lasting for 2 weeks or more in total than in those with fever for less than 2 weeks. Scarring was significantly more frequent in patients with severe renal involvement than in those with mild involvement, and scars developed at the sites of the most extensive lesions seen on the initial CT scans. Cortical scars were detected in 6 of the 7 patients in whom the lesions occupied 30% or more of the renal parenchyma. We conclude that the extent of the initial renal parenchymal involvement was the most important determinant of eventual scar formation.

Acute pyelonephritis without urinary tract obstruction usually responds favourably to antimicrobial treatment and it has been thought that renal scars and abscesses seldom develop in this condition (Smith, 1975). Computed tomography (CT) is a more sensitive technique for the detection of severe inflammatory renal disease than either intravenous urography (IVU) or ultrasound (Gold *et al.*, 1983; Soulen *et al.*, 1989). We have previously evaluated the relationship between CT findings, laboratory data, symptoms, and the course of the disease in patients with acute pyelonephritis (Tsugaya *et al.*, 1990). We found that the patients with recurrent febrile episodes took significantly longer to heal than those with a shorter febrile period. In these patients with recurrent fever, normalisation of the CT findings was markedly delayed despite the fact that laboratory tests showed improvement and flank pain subsided (Tsugaya *et al.*, 1990). It appears that in acute pyelonephritis the course of the disease differs widely between individuals, as does the risk of scar formation. In this study we used CT to observe the early stages of scarring in acute pyelonephritis and evaluated the factors associated with a higher risk of renal parenchymal scar formation.

Patients and Methods

Patients from the urology out-patient clinics of Nagoya City University Hospital and Anjo Kosei Hospital, who were diagnosed as having acute pyelonephritis without urinary tract obstruction, were admitted to the previously reported study between August 1984 and August 1987 (Tsugaya *et al.*, 1990). The patients gave informed consent to entry into the study and also consented to each CT scanning procedure.

All patients had chills, flank pain, a fever $> 38^{\circ}\text{C}$, tenderness in the costovertebral angle, pyuria, and a raised erythrocyte sedimentation rate and C-reactive protein level. Urine cultures were performed in all 14 patients and were positive in 11. The organism detected was *Escherichia coli* in 8 patients, *Klebsiella pneumoniae* in 2, and *Pseudomonas aeruginosa* in 1. Cultures were negative in the other 3 patients, although pyuria persisted in all of them, probably because antibacterial agents had been administered by other physicians before they were referred to us. Patients were excluded if they had urinary tract obstruction on IVU, evidence of urinary stones on a plain abdominal film, ultrasound or CT, or renal abscesses shown by CT or ultrasound examination. None of the patients had an underlying illness, except for 1 who had diabetes mellitus. Only those patients in whom

thorough follow-up investigations were undertaken were included in this analysis. The subjects were 13 women and 1 man who were aged from 18 to 70 years (mean 42.2, SD 16.1).

All patients were treated with antibacterial agents, being given the maximum recommended doses of latamoxef, cefazolin, cefotiam, cefaclor, or bacampicillin with or without amikacin, tobramycin, sulbenicillin, or ticarcillin for more than 6 days. After this initial treatment period, cinoxacin, pipemidic acid or sulfamethoxazole-trimethoprim were administered until CT changes could no longer be clearly detected, except in the case of 1 woman who was treated by a physician before we saw her. The positive urine cultures became negative in the 11 patients with such cultures after less than 2 weeks of treatment.

Each kidney was scanned completely by CT in sequential 1 cm slices, and scanning was repeated after the administration of intravenous contrast medium. When low density areas due to acute pyelonephritis were observed on the contrast scans, follow-up was performed until disappearance of the lesions was noted by repeat scanning after 1 month and thereafter at intervals of less than 4 months. Patients showing renal parenchymal atrophy on follow-up CT scans were diagnosed as having scarring. The follow-up period ranged from 40 to 440 days after the onset (mean 137.6, SD 109.4). In addition, an abdominal radiograph including the kidneys, ureters and bladder (KUB film) was taken immediately after the contrast CT and substituted for the IVU whenever possible. Otherwise, IVU was performed on another occasion.

CT findings were evaluated on the basis of the number and the distinctness of the low density areas seen in the kidneys, and the patients were classified into 2 groups. Grade 1 changes meant a total of 1 to 4 low density areas in both kidneys, and Grade 2 changes meant a total of 5 or more low density areas in both kidneys (or apparently liquefied very low density areas even if they did not show on the plain CT).

Low density areas seen on any particular slice that appeared to be associated with areas on the slices above and below were considered as one area. The most extensive low density areas and the area of the renal parenchyma on the same slice were measured on photographic enlargements and the percentage area of the renal parenchyma occupied by the lesions was calculated. Subjects were also classified into 2 groups according to the duration of fever. One group had fever of less than 2 weeks' duration and the other group had fever lasting a

total of 2 weeks or more. This group had repeated febrile episodes and the transient afebrile periods were also included in the calculated duration of fever. The extent of the renal scarring that occurred in association with each of these parameters was then evaluated. Statistical analysis was performed using the SAS statistical package. The Wilcoxon 2-sample test and the *t* test were used as non-parametric tests for comparisons of 2 groups.

Results

Scar formation was observed by CT in 6 of the 14 patients (Table). Examples of scar formation are shown in Figures 1 and 2. None of these 6 patients showing cortical scarring on CT scans had any abnormalities on IVU.

The clinical features of the patients are summarised in the Table. No relationship was seen between the organism causing pyelonephritis and the occurrence of scar formation. Serum creatinine levels were normal in all patients in this series.

Cortical scars were seen in 2 of the 9 subjects with fever of less than 2 weeks' duration, whereas scarring developed in 4 of 5 subjects febrile for more than 2 weeks in total. However, a statistical relationship between the duration of fever and the presence or absence of scarring was not observed. The small number of patients may have prevented this difference from being significant.

Scarring was observed to develop between 61 to 187 days after the onset of pyelonephritis and it took longer to develop in the patients with fever lasting 2 weeks or more than in those with fever for less than 2 weeks ($P < 0.05$). Scarring was seen in 6 of the 8 subjects with grade 2 lesions but was not observed in any of the 6 subjects with grade 1 lesions ($P < 0.01$). Scarring always occurred in the largest low density areas detected by CT. Scar formation was seen in 6 of the 7 patients in whom low density areas occupied 30% or more of the renal parenchyma on the CT slice showing the most extensive low density lesions ($P < 0.0005$).

Discussion

Several studies on renal scarring in vesicoureteric reflux have been reported previously, but those on the occurrence of scarring in pyelonephritis are relatively few. In general, IVU is used for the diagnosis of scar formation and the occurrence of scarring is determined by the detection of deformity of the calices or renal contour and assessment of the size of the kidneys (Smellie *et al.*, 1975). As

Table Details of Patients

Patient No.	Age (years)	Sex	Renal scarring	Urine culture	Duration of fever (days)	Side of lesions	No of lesions*	CT grade	Width of lesions (%)	Interval until renal scarring (days)
1	18	F	+	<i>K. pneumoniae</i>	49	L/R	8	2	42.0	113
2	46	F	+	<i>E. coli</i>	74	L/R	4	2	38.2	187
3	24	F	+	<i>E. coli</i>	35	L	5	2	33.8	161
4	33	F	+	<i>K. pneumoniae</i>	18	L/R	6	2	33.0	177
5	61	F	+	<i>E. coli</i>	3	R	5	2	40.7	68
6	65	F	+	<i>E. coli</i>	7	L	10	2	39.2	61
7	70	F	—	<i>E. coli</i>	8	L	6	2	37.2	—
8	34	F	—	<i>E. coli</i>	4	L/R	5	2	23.2	—
9	52	M	—	<i>Ps. aeruginosa</i>	5	R	4	1	18.3	—
10	56	F	—	<i>E. coli</i>	6	L/R	4	1	14.0	—
11	30	F	—	Negative	16	R	2	1	9.3	—
12	36	F	—	Negative	10	R	2	1	9.7	—
13	35	F	—	Negative	5	R	1	1	8.6	—
14	31	F	—	<i>E. coli</i>	10	L	1	1	5.2	—

* The number of lesions demonstrated as wedge-shaped low density areas on CT scans.

M = male, F = female, L = left, R = right, L/R = bilateral

shown in this study and our previous study in patients with vesicoureteric reflux (Tsugaya *et al.*, 1989), cortical scarring without caliceal deformity cannot be diagnosed by IVU alone because the scar is seldom located in a position where it can be recognised by this method. It has been generally assumed that acute pyelonephritis usually heals without renal scarring (Smith, 1975), but scarring has sometimes been reported in a considerable percentage of these patients (Meyrier *et al.*, 1989; Soulen *et al.*, 1989). The occurrence of cortical scarring or renal atrophy after acute pyelonephritis has been reported in 37% (Meyrier *et al.*, 1989) and 50% (Soulen *et al.*, 1989) of patients respectively. In the present series, 42.9% of patients developed scarring, an incidence similar to that of previous reports.

Meyrier *et al.* (1989) reported that cortical notching could be detected within a month of the onset of illness, while our study showed that cortical scars became visible more than 2 months after the onset. Follow-up CT scans took longer to confirm scarring in the subjects with fever that lasted for 2 weeks or more. These subjects had repeated exacerbations of their pyelonephritis and it was considered that the appearance of scarring was delayed because of the slow resolution of inflammation.

Acute lobar nephronia (acute focal bacterial nephritis) may lead to cortical scarring, although Rosenfield *et al.* (1979) reported that focal scars were found in only 2 of 12 patients with this

condition. Renal bacterial infection spans a continuum of severity from acute pyelonephritis through progressively worsening stages of interstitial inflammation to frank abscess formation. It can be a multifocal process, with different portions of the kidney exhibiting different degrees of inflammation. A confusing variety of terms have been used to describe the various stages of inflammation, e.g. focal pyelonephritis, focal and diffuse acute bacterial nephritis, lobar nephronia, and the pre-abscess state (Soulen *et al.*, 1989).

Hypodense areas on CT scans performed after the administration of intravenous contrast medium have been shown to correspond histologically to severe oedema, polymorphonuclear leucocyte infiltration and abscesses (Meyrier *et al.*, 1989). We found a significant relationship between the grade of the CT changes and the development of scarring, as would probably be expected, since extensive inflammation is more likely to leave residual effects than mild inflammation. In the patients with multifocal lesions, some progressed to cortical scars while other lesions of the same kidneys healed without scarring. When we investigated which lesions were likely to produce scarring, we found a significant relationship between the formation of cortical scars and the percentage of the renal parenchymal area occupied by hypodense lesions on the most extensively affected CT slice.

Previous experiments have shown that the severity of renal scarring in pyelonephritis parallels the intensity of the acute exudative processes

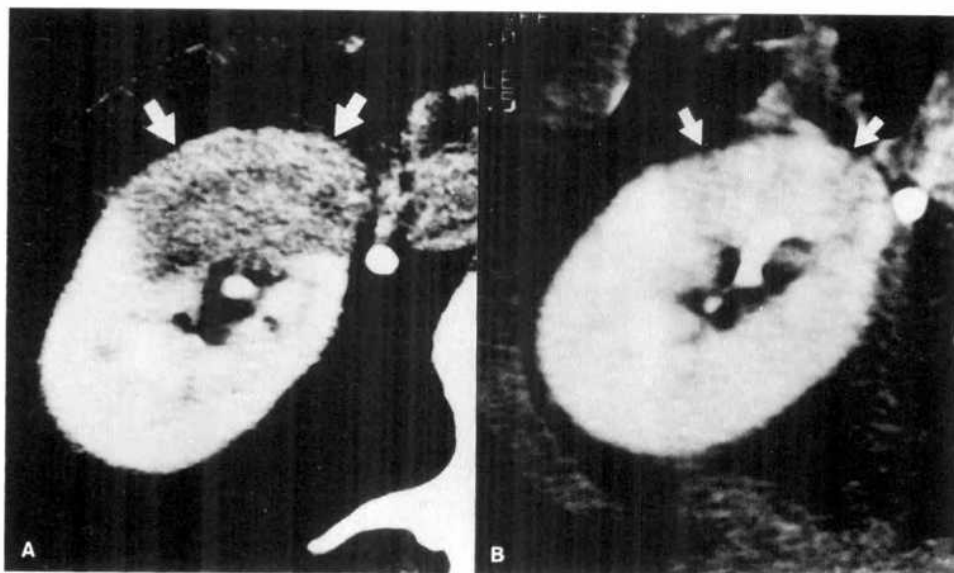


Fig. 1 Cortical scarring in 46-year-old woman with 74-day history of febrile episodes. (A) Lesion indicated by arrows was caused by pyelonephritis and was confirmed as low density area by contrast CT 2 weeks after the onset of her illness. This was the most severe lesion. Multifocal lesions were present in both kidneys. (B) Contrast CT 6 months later shows renal parenchymal atrophy at the site of the previous lesion (arrows).

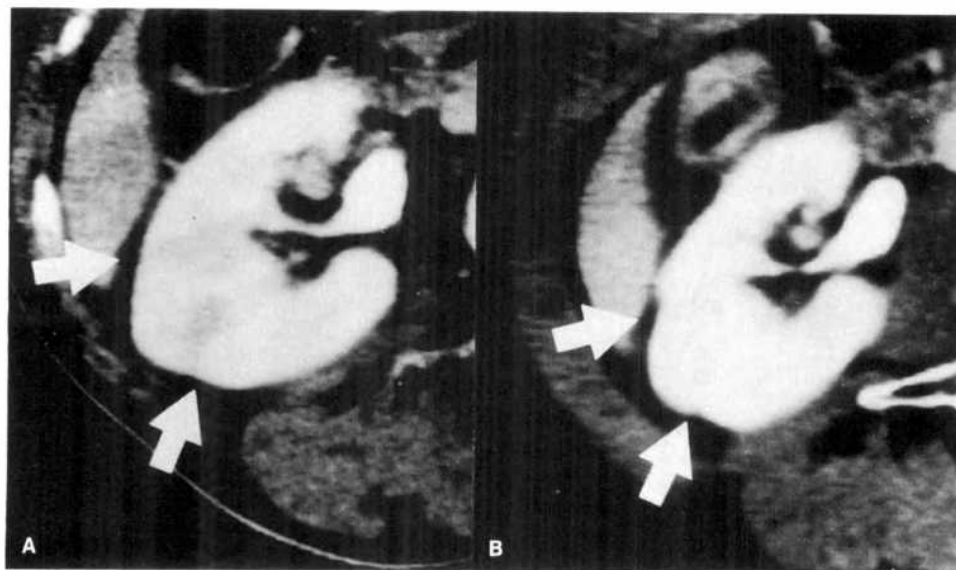


Fig. 2 Cortical scarring in 61-year-old woman with 3-day history of fever. (A) Lesions indicated by arrows were confirmed as low density areas by contrast CT 4 days after the onset of the illness. (B) Contrast CT 2 months later shows cortical scarring (arrows).

(Glauser *et al.*, 1978). It has been demonstrated that the infiltration of leucocytes into infected kidneys is associated with destruction of the tubular basement membrane and the tubular epithelium, and that the most extensive tissue damage occurs at the site of maximum leucocyte infiltration (Slotki and Asscher, 1982). These observations suggest that the event which triggers the scarring process is the initial interaction of invading pathogens and the response of the host inflammatory cells. Such a concept would be consistent with our findings in this study.

Cortical scarring was seen in 6 of the 7 patients in whom hypodense areas occupied 30% or more of the renal parenchyma. In the 1 case where cortical scarring was not observed despite the presence of extensive low density areas, the lesion was in the upper pole of the kidney where the parenchyma is thin and this may have falsely enlarged its percentage area. In addition, a scar forming in this region would be difficult to detect by transverse CT scanning.

Four of 5 patients with fever lasting 2 weeks or more had clear and extensive hypodense areas on CT scans, and the healing of their renal lesions showed a considerable delay (Tsugaya, 1990). The formation of cortical scars was also far slower in this group. The delay in healing and in the formation of scarring was possibly related to repeated relapses due to insufficient initial treatment and might also have reflected the severity of the renal lesions.

In 1 patient, pyelonephritis recurred approximately 1 year after the initial CT scan was obtained and the reinfected lesion was in almost the same area as that on the initial CT scans. Cortical scarring and atrophy of the renal parenchyma showed further progression on the follow-up CT scan obtained after reinfection (Tsugaya, 1989). Although it is not possible to draw any general conclusions from experience with one case alone, this was an interesting finding since it suggests that areas once subjected to infection are likely to be reinfected with further scarring and that such a process may lead to the development of extremely fibrous renal scarring.

In conclusion, this study has shown that follow-up CT scanning will sometimes reveal renal cortical scarring that is not detectable by conventional radiography following acute pyelonephritis, and that extensive lesions on the initial CT scans which

occupy 30% or more of the renal parenchyma are likely to be found in patients with a long duration of fever and are more likely to progress to cortical scars.

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Urinary Tract Metastasis from Renal Carcinoma

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Summary—Five patients with urinary tract metastases from renal carcinoma are presented. In 4, urinary tract metastasis occurred in the absence of spread elsewhere. The initial presentation in 1 patient was ureteric obstruction; 3 others re-presented with haematuria and the fifth patient was diagnosed post mortem. Metastatic sites included ipsilateral ureter, contralateral ureter, ureteric stump, bladder and prostatic fossa.

After previous nephrectomy for renal carcinoma, urinary metastases, although rare, should be considered and investigation of unexplained haematuria should include the ureteric stump. Useful palliation and possibly cure can be achieved by resection of these lesions.

The unpredictable biological behaviour and metastatic propensity of primary renal carcinoma are both well recognised. Lung, bone and lymph node are the common sites for metastatic spread of this neoplasm. Occasionally renal carcinomas are associated with solitary metastases either at presentation or after a period of follow-up and in such cases excision of the metastasis can be justified. Metastasis of primary renal carcinoma to other sites in the urinary tract is uncommon, and rare when it occurs in the absence of spread elsewhere. We report 5 cases of renal carcinoma with metastasis to other sites in the urinary tract. In all but 1 of these cases there was no evidence of spread elsewhere.

Patients and Methods

There were 2 female and 3 male patients whose median age at initial presentation was 59 years (range 48–65). Patients were identified from the pathology records of the Institute of Urology. Details are summarised in the Table.

Three patients presented with right-sided renal tumours unassociated with any evidence of distant metastasis and underwent radical nephrectomy. Urinary tract recurrences were subsequently diag-

nosed after follow-up periods of 35, 38 and 52 months. All 3 re-presented with haematuria, investigation of which included intravenous urography and cystoscopy.

Recurrence developed in the ipsilateral ureter in 2 of these patients. In patient 1 the lesion was in the mid ureter and was diagnosed by stump ureterography only after initial cystoscopy had been negative and a second cystoscopy had revealed blood at the ureteric stump orifice. In patient 2 recurrent disease was found at and around the ureteric orifice at cystoscopy and transurethral resection was performed. A corresponding tumour mass was apparent on computed tomography (Fig.). In neither case was there evidence of metastatic disease elsewhere and both patients therefore underwent excision of the ureteric stump with partial cystectomy. In one of them an augmentation ileo-cystoplasty was performed. Histology confirmed metastatic renal carcinoma in both cases. The first was lost to follow-up a year later with suspected recurrence in the retroperitoneum and is believed to have subsequently died from disseminated disease. The second remained disease-free for 2 years following excision of the metastasis but then re-presented with an isolated contralateral adrenal metastasis.

The third patient re-presented with an apparently solitary 1-cm diameter metastasis in the contralateral mid ureter apparent on intravenous urography.

Table Clinical Details of Urinary Tract Metastases from Primary Renal Carcinoma

Patient no.	Age (years)	Site	Symptom	Time from nephrectomy (months)	Treatment	Outcome
1	65	Ureteric stump	Haematuria	52	Stump ureterectomy and partial cystectomy	Lost to FU with recurrent disease
2	55	Bladder and ureteric stump	Haematuria	35	Stump ureterectomy and partial cystectomy	Contralateral adrenal metastasis 2 years later
3	59	Contralateral ureter and kidney	Haematuria	35	Local ureteric excision and upper pole nephrectomy	Widespread disease 1 year later
4	48	Ipsilateral ureter	Obstruction	Initial presentation	Local excision then nephrectomy	Disease-free 7 years later
5	64	Bladder and prostate	Advanced inoperable renal carcinoma diagnosed 5 months following transvesical prostatectomy. Urothelial metastases confirmed at post mortem			

She underwent a conservative ureteric resection with anastomosis. Three months later, however, investigation of further haematuria revealed a 2-cm upper pole renal tumour on arteriography. An upper pole nephrectomy was therefore performed and histology again showed renal carcinoma. During this operation a separate 1-cm nodule at the renal hilum was also removed and histology showed this to be an encapsulated clear cell tumour of renal origin. Nine months later she presented with metastatic renal carcinoma in the breast and shortly after this widespread bony metastases supervened.

The fourth patient presented with a small mid-ureteric tumour which was obstructing his left kidney. A conservative ureteric resection with end-to-end anastomosis was performed and histology suggested a metastatic tumour with renal carcinoma as the most likely primary site. An ipsilateral renal tumour was subsequently diagnosed, there being no evidence of metastasis elsewhere. A radical nephrectomy was therefore performed and renal carcinoma confirmed. The patient remains well and disease-free after 7 years' follow-up.

The fifth patient presented with haematuria 3 months following a transvesical prostatectomy. He was found to have a large left renal tumour with multiple pulmonary metastases, deteriorated rapidly and died. At post mortem a locally advanced renal carcinoma with pulmonary and bone metastases was confirmed. There was a large metastasis in the bladder related to the transvesical prostatectomy scar and the prostatic bed was also infiltrated with metastatic renal carcinoma; however, the ureters were tumour free.



Fig. CT scan showing recurrent renal carcinoma involving bladder in patient No. 2

Discussion

In the absence of local tumour invasion, both the urinary bladder and ureter are rare sites for secondary tumours. Less than 2% of all bladder tumours are metastases (Roberts, 1978) and, of these, melanoma, breast and stomach are well recognised distant primary sites. Metastasis to ureter, other than by direct invasion, is also rare, the gastrointestinal tract, uterine cervix and melanoma all being recognised as potential primary sites for such spread.

In a post mortem study of 1451 cases of renal adenocarcinoma Saitoh (1981) reported the incidence of bladder and ureteric metastases as 2% and 1% respectively, but there were apparently no cases with spread to the prostate. There was only 1 case with an isolated ureteric metastasis and only 1 other with an isolated bladder metastasis.

Twenty cases of isolated bladder wall metastasis from renal adenocarcinoma and some 45 cases of ureteric involvement have been previously reported in the literature (Remis and Halverstadt, 1986; Psirhamis, 1987). In a majority of these cases widespread disease was either present at the time of diagnosis of the urinary tract metastasis or else developed soon after. In the remaining cases follow-up periods were too short to allow comment on long-term survival following surgical excision. Of interest is that solitary ureteric and bladder metastases have been reported as late as 6 and 8 years respectively after nephrectomy.

There has been much speculation as to the mode of spread responsible for the genesis of urinary tract metastases. Direct spread was not seen in our cases and rarely observed in previous reports. The mechanisms of spread considered have included endoluminal, bloodborne or via lymphatics. Malignant cells may be detected in the urine of patients with renal carcinoma and presumably this is more likely if there is a breach of the renal pelvis. It has been suggested that tumour manipulation during nephrectomy prior to ureteric ligation may further promote the shedding of such cells into the urinary stream. The evidence from our fifth patient, who had metastatic renal adenocarcinoma in a bladder scar and in the prostatic fossa following transvesical prostatectomy, suggests that, in the presence of a breach in the urothelium, exfoliated renal carcinoma cells can implant and grow as metastatic lesions elsewhere in the urinary tract. It has been suggested and is conceivable that lesser degrees of urothelial trauma such as preliminary retrograde pyelography might also predispose to such implantation (Seppanen and Willenius, 1970).

The blood stream, however, is a more common mode of spread for renal carcinoma and there seems no reason why the occasional metastasis should not be established by this route in either ureter or bladder. The synchronous finding of widespread disease in many of the cases reported previously and the finding of contralateral ureteric disease in our third case lend support to this view. It has also been proposed that urinary tract metastasis can occur as a result of retrograde venous spread of tumour emboli and that this is predisposed to by

tumour growing along and obstructing the renal vein (Mitchell, 1958).

Isolated urinary tract metastases from renal carcinoma, though rare, pose a diagnostic and management problem. The ureteric stump should not be overlooked in the investigation of patients presenting with haematuria after previous nephrectomy. While the prognosis for these patients must be guarded because isolated urinary tract metastasis may herald widespread disease, surgical intervention is justified since long-term survival is possible, as in our fourth patient, and in others useful palliation can be achieved. Therefore, if investigation excludes the presence of spread elsewhere, solitary urinary tract metastases should be treated like other solitary metastases from renal carcinoma and, if feasible, be resected. In the bladder transurethral resection may be adequate for smaller metastases; however, stump ureterectomy with or without partial cystectomy is appropriate for ureteric stump recurrences.

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Ureteric Stone Management Using a Second Generation Lithotripter

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Summary—A series of 209 consecutive patients with ureteric calculi underwent 296 extracorporeal shock wave lithotripsy treatments on the Siemens Lithostar over a 25-month period; 123 stones were upper ureteric, 30 mid-ureteric and 56 lower ureteric; 46.9% were right-sided stones, 53.6% were left-sided and 0.5% (1 patient) were bilateral. On referral, 60 patients had stents and 15 had nephrostomies for obstruction. All treatments were performed without anaesthesia except for 9 patients in whom stent insertion or ureteroscopic manipulations were attempted concomitant to ESWL.

The average number of treatments was 1.42, with 27.5% of patients requiring more than 1 treatment. The average number of shocks per treatment was 3995 and the average hospital stay was 1.79 days. Complete clearance of the stone was achieved in 82% of upper ureteric stones, 89% of mid-ureteric and 80% of lower ureteric stones.

The facility for X-ray localisation of stones allows a high proportion of ureteric calculi to be treated successfully by ESWL, including the more taxing middle and lower ureteric calculi.

The introduction of extracorporeal shock wave lithotripsy (ESWL) has greatly influenced the management of urinary tract calculi. Soon after its introduction, ESWL was attempted (with little success) for upper ureteric calculi which were large and often impacted (Schmiedt and Chaussy, 1984). The initial disappointing results of *in situ* ESWL treatment led some authors to suggest manipulation of the calculus into the pelvis prior to lithotripsy (Dretler *et al.*, 1986), following which a success rate of 70% was achieved (Mueller *et al.*, 1986). The best results were obtained with upper ureteric calculi, with middle ureteric calculi presenting more difficulties especially when overlying the posterior bony pelvis. Some centres using the Lithostar reported the necessity of primary endoscopic manipulation for the latter (Thornhill *et al.*, 1990). Lithotripsy for distal ureteric calculi presented a problem on the Dornier HM3 because of difficulty in positioning

the stone in the focus (Miller *et al.*, 1986). Lithotriptors using ultrasound for localisation reported even more disappointing results owing to inability to visualise the stone adequately in the middle and distal ureter (Smidt *et al.*, 1990). Manipulation has its risks and limitations. The same authors reported that 80% of upper ureteric calculi may be mobilised with endourological techniques which, in addition to being more invasive and involving general anaesthesia, carry the risks of septicaemia and ureteric damage leading to stenosis.

A second generation lithotripter (Siemens Lithostar) using X-ray localisation has been in use in this unit for the primary treatment of ureteric stones *in situ*.

Patients and Methods

The study group comprised 209 consecutive patients with ureteric calculi who were treated on the Siemens Lithostar in this unit from April 1988 to May 1990. The Lithostar is a second generation

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lithotripter. The shock wave is produced by electromagnetic generation of a high voltage current pulsed through a coil in the base of the shock head. This wave is focussed by an acoustic lens, creating a high-intensity focal zone. The total energy per pulse and the width of the high intensity focal zone in the Siemens Lithostar are intermediate between the spark-gap and the piezoelectric systems (Coleman and Saunders, 1989). The shock wave generator setting for the Lithostar is a voltage value (kV) with high voltage settings producing the highest peak pressures. The localisation system for the Lithostar is via 2 X-ray tubes, antero-posterior and 40° oblique providing accurate localisation for radio-opaque calculi.

Ureteric calculi were divided into upper, middle and lower calculi according to the following definition:

Upper ureter: from the pelviureteric junction to the transverse process of L3.

Middle ureter: from the transverse process of L3 to the lower level of the os sacrum.

Lower ureter: from below the bony pelvis to the vesicoureteric junction.

Upper ureteric calculi were treated supine, middle ureteric calculi were treated prone and the majority of lower ureteric calculi were treated prone, though some patients in the latter group had to be positioned semi-prone or supine owing to obesity or interposition of the bony pelvis in the path of the shock wave.

There were 155 males (75%) and 54 females (25%). The age of the patients ranged from 17 to 90 years with an average of 53.6; 97 stones (46.9%) were right-sided and 111 (53.6%) were left-sided, with only 1 patient (0.5%) who had bilateral ureteric calculi treated on 2 different occasions. The average duration from the time of referral to the start of treatment was 7 weeks; 151 patients (73%) were treated as day cases and 56 (27%) as in-patients. The total hospital stay ranged from 1 to 8 days with an average of 1.79.

Stone size ranged from 4 to 25 mm (average 8) in the longest diameter for upper ureteric calculi. Mid-ureteric calculi ranged from 3 to 16 mm (average 8.8). Lower ureteric calculi ranged from 5 to 16 mm (average 7.6).

The treatment policy was a minimally invasive technique: primary ESWL *in situ* for ureteric calculi presenting with pain or obstruction. Patients received 75 mg diclofenac and 20 mg temazepam orally about 30 min before treatment as a premedication. A total of 60 patients had ureteric stents

inserted prior to referral: 46 for upper ureteric calculi, 8 for mid-ureteric calculi and 6 for lower ureteric calculi. A general anaesthetic was administered to 9 patients at first treatment; 1 had ureteroscopy, 6 had ureteric stents inserted and 1 patient had both.

Results

The number of patients in each category and the percentage of obstructed ureters prior to primary ESWL is shown in Table 1. Although the total number of obstructed ureters was 101, only 60 patients (60%) had ureteric stents inserted on referral to this centre. Fifteen patients had nephrostomies as primary treatment for obstruction prior to referral. Of these, 13 were for upper ureteric calculi and 2 for lower ureteric calculi. If ureteric obstruction was only partial (a dilated system on the intravenous urogram with partial hold-up but the dye passing down the ureter), and lithotripsy could be performed within a few days of referral, ureteric stenting was sometimes not carried out.

Table 1 Number of Patients in each Category and Incidence of Obstruction

Site	Upper (%)	Middle (%)	Lower (%)
Obstructed	71 (57.7)	10 (33.3)	20 (35.7)
Non-obstructed	52 (42.3)	20 (66.7)	36 (64.3)
Total	123	30	56

Table 2 shows the average number of treatments for each category. The re-treatment rate was almost identical; 34 patients (27.6%) with upper ureteric calculi, 8 (26.6%) with middle ureteric calculi and 15 (26.7%) with lower ureteric calculi required more than 1 treatment. The average number of shocks per treatment for all 3 categories was 3995. The number of treatments for any one stone ranged from 1 to 5 (average 1.42). The average treatment time was 74 min. The kV setting for the machine ranged from 16.0 to 19.0 kV (average 18.4). The

Table 2 Number of Treatments per Category

Site	Upper (%)	Middle (%)	Lower (%)
No. of treatments			
1	89 (72.3)	22 (73.3)	41 (73.2)
2	20 (16.3)	5 (16.7)	11 (19.6)
> 2	14 (11.4)	3 (10.0)	4 (7.1)

average screening times per treatment for the 3 categories were 1.98 min for upper, 2.01 min for middle and 1.93 min for lower ureteric calculi. Clinically, higher settings are used most often. Pre-treatment auxiliary procedures included 60 stents and 15 nephrostomies. Thus 36% of ureteric stones required pre-treatment auxiliary manoeuvres. Of the 60 patients with stents, 36 (60%) were stone-free. Therefore the presence of a stent did not increase the stone rate, probably because of the concomitant decreased ureteric motility.

Table 3 shows the number of patients who were stone-free 3 months after ESWL. Stone-free was defined as complete absence of fragments on a plain abdominal X-ray or an intravenous urogram for radiolucent stones. Since the Lithotripter Unit in Bristol is a referral centre, the 3-month follow-up was available (either by examining the X-rays or by questionnaire) in only 175 of the 209 patients (84%). Complete clearance of the stone was achieved in 82.8% of all ureteric stones in which follow-up had been completed.

Table 3 Number of Patients Stone-free after 3 Months

Site	No. of patients	Stone-free (%)
Upper	100	81 (81)
Middle	27	24 (89)
Lower	48	39 (80)
Total	175	145 (82.8)

The complications following treatment according to category are shown in Table 4. The overall complication rate was 14.8%, with very few major complications requiring intervention.

The action needed for each complication is summarised in Table 5.

Table 4 Complications According to Category

Complication	Upper	Middle	Lower
Colic	4	2	3
Pyrexia	—	—	—
Urinary tract infection	3	—	—
Haematuria	—	—	2
Septicaemia	—	—	1
Steinstrasse	—	—	1
Obstruction	7	2	2
Total	14	4	9

Overall complication rate 14.8%

Table 5 Action Required for Complications

	Upper	Middle	Lower	Total
Antibiotics	1	—	3	4
Nephrostomy	—	—	1	1
Ureteroscopy	3	2	4	9
Stent insertion	4	—	1	5
Open surgery	1	1	—	2
Basket	1	—	1	2

Discussion

This study has confirmed that extracorporeal shock wave lithotripsy is as an effective modality for the management of upper ureteric calculi. Initially, it was suggested that the push/bang technique resulted in a higher success rate (Miller *et al.*, 1985). This was thought to be due to the expansion chamber surrounding the stone (Dretler *et al.*, 1986). However, retrograde manipulation usually requires a general or regional anaesthetic, which is associated with its own morbidity, in addition to the risk of ureteric perforation and sepsis or ureteric damage leading to stenosis. In this study, the 3-month stone clearance rate for upper ureteric calculi was 82%, with 72.3% of patients requiring only 1 treatment.

Mid-ureteric calculi presented more formidable problems for lithotriptors owing to the interposition of bone in the path of the shock waves. Patients are treated prone on the Lithostar, achieving coupling with the shock head by contact through the abdominal wall. X-ray localisation of the stone in the middle ureter is usually achieved relatively easily, though it requires a more experienced operator who needs to be more familiar with the machine since the fluoroscopic image is sometimes not as clear. The highest success rate was achieved in this category, with 89% of patients stone-free after 3 months and 73% of them requiring only 1 treatment. This could be attributed to less movement of the stone in the focal zone during respiratory movements and also less intervening tissue between the shock head and the stone in the prone position causing less attenuation of the shock waves.

The treatment of lower ureteric calculi remains controversial. Several issues need to be addressed when choosing between ESWL and ureteroscopy. This includes pain, the need for anaesthesia, the need for multiple treatments, cost and convenience (Dretler, 1990). ESWL is not performed on young women in the child-bearing period if pregnancy is suspected, although there has been no evidence of

mutagenic effects of ESWL *in utero* (Mendoza *et al.*, 1991). In this study, 80% of patients with lower ureteric calculi were stone-free after 3 months and 73.2% of these needed only a single treatment.

In conclusion, extracorporeal shock wave lithotripsy is a safe and effective primary treatment for upper, middle and lower ureteric calculi. It has a high success rate, an acceptable incidence of auxiliary procedures requiring general anaesthesia and few severe complications. Minor complications of *in situ* ESWL were infrequent and were all treated successfully. This low complication rate could be attributed to the policy of adopting a minimally invasive technique.

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Calcium Balance, Growth and Skeletal Mineralisation in Patients with Cystoplasties

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Summary—Twelve adult female patients and 16 children who had undergone augmentation cystoplasty at least 2 years previously were studied to assess calcium balance and skeletal mineralisation.

The serum and 24-h urinary calcium levels were measured and arterial blood gas analysis was performed in all patients. In children, skeletal mineralisation was assessed by serial study of their growth charts, comparing their growth centiles before and after cystoplasty. In adults, skeletal mineralisation was assessed by dual photon absorptiometry (DPA).

As previously reported, all patients had a metabolic acidosis, usually with respiratory compensation. Serum and 24-h urinary calcium levels were all within the normal range. Growth charts of the 6 children with colocolocystoplasties showed an average of 20% reduction in growth potential in 3 of them. Growth charts in the 10 children with ileocolocystoplasties did not show any change in growth pattern. DPA bone scans in adults were all normal.

These results suggest that if calcium is mobilised from bone in patients with a cystoplasty as a result of the metabolic acidosis, then it is reabsorbed from the bladder by the gut segment after an ileocolocystoplasty; colonic segments are less efficient than ileal segments, however, so that after a colocolocystoplasty skeletal demineralisation or a reduction in growth potential is more likely.

We have previously shown that after interposition of an intestinal segment into the urinary tract, metabolic acidosis occurs, usually with respiratory compensation (Nurse and Mundy, 1989a). Although not dramatic, the consequences of metabolic acidosis can be serious in the long term, particularly with respect to skeletal mineralisation. One possible consequence of long-term metabolic acidosis could therefore be a failure to grow normally in children, or skeletal demineralisation in adults.

The aim of this study was to see whether there is any evidence that this does indeed occur.

Patients and Methods

The 2 most vulnerable groups, and those most likely therefore to show a problem of skeletal mineralisation, are growing children and women around the time of menopause. We therefore studied 16 children who had had a cystoplasty before the age

of 10 and whose height had been measured on at least 2 occasions pre-operatively, and 12 women who had had a cystoplasty between the ages of 45 and 50. In all patients the operation had been performed at least 2 years previously. Only fully mobile patients were included in both groups to exclude those who might be expected to have a pre-existing abnormality of skeletal mineralisation. The majority of patients had undergone ileocolocystoplasty but 6 of the children and 2 of the adults had had a sigmoid colocolocystoplasty. All patients were asymptomatic.

Serum calcium and 24-h urinary calcium levels were estimated in both groups and acid-base balance was assessed by arterial blood gas analysis. In the children the state of the skeleton was assessed by studying growth charts before and after cystoplasty to see whether they continued to grow along the same centile or whether this changed, in the same way that growth charts are used to monitor bone disease in children with renal failure (Broyer, 1982). In adult patients growth velocity obviously

cannot be used, so skeletal mineralisation was assessed by dual photon absorptiometry (Wahner, 1987), the assumption being that skeletal mineralisation was normal pre-operatively.

DPA is a very accurate technique for measuring the bone mineral content of the trabecular bone of the axial skeleton and specifically the lumbar vertebrae and the femoral neck, where bone loss tends to occur preferentially (Mazess, 1984). The technique depends on the attenuation of radioisotopically emitted monochromatic radiation as it passes through tissues. When 2 different photon energies are emitted, the attenuation due to the soft tissues can be subtracted from the attenuation due to bone so that bone mineral content, computed as grams of hydroxyapatite equivalent, or bone mineral density, in grams/cm² of area scanned, can be derived (Mazess, 1984; Wahner, 1987).

Results

Arterial blood gas analysis confirmed that metabolic acidosis, with or without respiratory compensation, occurred in all patients.

In all patients the serum calcium and 24-h urinary calcium levels were within the normal range.

In adults, DPA bone scans were all normal. All children with ileocystoplasties continued to grow along the same centile as before their cystoplasty. However, 3 of the 6 children with colcystoplasties showed a substantial fall-off in the rate of growth following their cystoplasty, averaging 20%. No significant change was observed in the weight centile.

Discussion

The retrospective nature of this study and the small number of patients studied mean that the findings must be interpreted with caution. The results suggest that after a colcystoplasty growing children may fail to achieve their growth potential because of metabolic acidosis. Why this affects only some children is not clear. Presumably in all patients with an intestinocystoplasty calcium carbonate is mobilised from bone to act as a buffer because of the metabolic acidosis that follows; the carbonate combines with the hydrogen ions and the calcium is excreted in the urine (Goodman *et al.*, 1965). When an ileocystoplasty has been performed, however, the ileal segment is theoretically able to reabsorb the calcium from the urine, thereby maintaining normal or near normal calcium balance and skeletal mineralisation, particularly in adults,

whereas a segment of sigmoid colon in a patient with a sigmoid colcystoplasty is less efficient, assuming that the absorptive characteristics of bowel when used as a cystoplasty mirror their characteristics in the normal situation. We are currently testing this hypothesis by studying the absorption of radiolabelled calcium in such patients.

We have also seen 2 cases of clinically overt hypokalaemia developing in patients with colcystoplasties and a reduction of total body potassium (and not just serum potassium) has been confirmed in these 2 patients by total body potassium scanning. Whether this is related to potassium secretion by the colonic segment used for the cystoplasty or, more probably, whether this too is a consequence of the metabolic acidosis (Batlle, 1989) is not clear and obviously requires further investigation. We have found no evidence of total body potassium depletion after ileocystoplasty and, as with calcium, we suspect that this is because the ileal segment reabsorbs potassium from the urine in the bladder.

Other than indicating that further studies of both calcium and potassium absorption need to be done in patients with ileocystoplasty and with colcystoplasty, these findings support the view that ileum is preferable to colon for a cystoplasty. Other studies of the incidence of bacteriuria and the potential incidence of malignancy in patients with a cystoplasty also suggest that ileum is preferable to colon (Nurse and Mundy, 1989b). The findings also suggest that although we found no evidence of overt skeletal demineralisation or failure to grow normally in patients with ileocystoplasty, the metabolic acidosis should be taken seriously and treated by regular oral bicarbonate in all patients with a cystoplasty rather than ignored, which seems (in discussion with colleagues) to be current practice in many units at the present time.

The adverse metabolic effects of uretero-sigmoidostomy have been established and well investigated since the report by Ferris and Odel in 1949, but there has been comparatively little study of the effects of other similar urological procedures, although there seems no reason why interposition of an intestinal segment into the urinary tract should not produce the same or similar metabolic effects however it is interposed, depending far more on the surface area and the type of the bowel segment used.

After ureterosigmoidostomy a chronic hyperchloraemic acidosis develops, leading to hypokalaemia and to skeletal demineralisation. This has been described repeatedly in man and more recently

studied in experimental animals (Koch and McDougal, 1985; McDougal *et al.*, 1988; Koch *et al.*, 1990). Similar findings have been reported by Caprilli *et al.* (1980) in patients with rectosigmoid bladders. By contrast with these instances of colonic interposition, the incidence and severity of metabolic disturbance after ileal interposition, typified by ileal conduit urinary diversion or ileocystoplasty, seem much less, although they do occur (Goldwasser and Webster, 1986).

In general, the conclusions of most studies are that it is the surface area of the reabsorbing mucosa that determines the degree of any metabolic disturbance and that as the surface area of a cystoplasty is considerably smaller than that of a ureterosigmoidostomy, a metabolic disturbance should not occur (assuming normal or near normal renal function). This view, however, takes no account of the chronicity of the exposure to urine, or of qualitative and quantitative differences in absorptive characteristics between different intestinal segments, both of which we feel are just as important. We have previously shown (Nurse and Mundy, 1989a) that gut tends to behave like gut with little or no change for many years after a cystoplasty, if not for ever. We feel, therefore, that a more pertinent question, if all intestinal interpositions can cause a chronic metabolic acidosis, is why the adverse consequences of this are not seen more commonly or more dramatically.

One possible reason why we have not found more dramatic changes of skeletal demineralisation after ileocystoplasty, and indeed after colocolocystoplasty perhaps, is because skeletal demineralisation often takes many years to develop with chronic metabolic acidosis. It is possible, therefore, that if the present study were to be repeated in 5 years' time in the same group of patients, the results might be more striking. The gradual nature of the process might also explain why there were no obvious changes in the serum or urinary calcium levels. A more detailed prospective study of these parameters is currently under way to investigate this possibility.

A further problem that needs to be resolved is whether or not right colon has different absorptive characteristics from sigmoid colon. The importance of this relates to patients requiring substitution cystoplasty. Substitution cystoplasty requires a much larger piece of bowel than augmentation cystoplasty and also requires it to be mobilised to a greater degree so that it will reach down to the floor of the pelvis for anastomosis to the bladder neck or membranous urethra. Ileum cannot always be mobilised to this degree, whereas the colon always

can. Furthermore, the colon is nutritionally expendable, so that a long length can always be sacrificed for cystoplasty, whereas ileum is nutritionally much more important and one can therefore not so readily sacrifice the 70 cm or so that are required for a cystoplasty, particularly in a child. For these reasons ileum is less satisfactory than the right colon for substitution cystoplasty. If the effects of acidosis can be mitigated in patients with a substitution colocolocystoplasty by the administration of oral bicarbonate, or if the right colon is not as prone as the sigmoid colon to lead to disordered calcium homeostasis, then growth problems in children with colocolocystoplasties may not be so likely to occur.

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Cystectomy and Substitution Enterocystoplasty: Alternative Primary Treatment for T2/3 Bladder Cancer

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Summary—The optimal treatment for invasive bladder cancer remains controversial. Although external beam radiotherapy is able to eradicate the disease in a number of patients, the difficulty is selecting those who will respond. Those who do develop a local recurrence will require a salvage cystectomy combined with urinary diversion. The results of performing cystectomy and bladder reconstruction as a primary procedure are presented and the concept of combining this with chemotherapy as an alternative strategy for the management of bladder cancer is discussed.

The current favoured primary modality of treatment for invasive bladder cancer in the United Kingdom is radical external beam radiotherapy (EBRT). If local disease recurs or the patient fails to respond to EBRT, salvage cystectomy has been shown to be a safe and effective method of disease control (Hendry, 1986). However, the recent resurgence of interest in urinary tract reconstructive procedures, which can preserve continence and potency, has led to a reappraisal of this treatment strategy for certain selected groups of patients with bladder cancer (Reddy *et al.*, 1987; Light and Marks, 1990). Combined nerve-sparing cystectomy and cystoplasty aims to eradicate the need for an incontinent abdominal stoma, with its attendant psychosocial implications, without adversely affecting the patient's prognosis and without the patient being exposed to the hazards of radiotherapy. We report our experience of performing cystoplasty with preservation of the normal urethral outlet in patients with primary malignant bladder disease.

Patients and Methods

Thirteen male and 4 female patients with malignant disease were selected for reconstruction between November 1987 and May 1991. Their mean age

was 49 years (range 24–64) and the tumour types are shown in Table 1. The patients were selected according to the histological type of the tumour, its stage and position, the age and sex of the patient, and the presence or absence of previous radiotherapy. All tumours were T2–4 and G2–3, except for 2 patients. One was aged 24 and had developed a localised adenocarcinoma and an area of carcinoma *in situ* within a bladder affected by cyclophosphamide cystitis. The other was aged 58 and had a total bladder replacement for a carcinoma *in situ* in which there was urethral sparing. Tumours other than transitional cell carcinomas were selected because of their known relative resistance to radiotherapy (Richie *et al.*, 1976; Thomas *et al.*, 1971). The 2 patients with squamous cell carcinomas had both had previous infection with schistosomiasis. Transitional tumours were present in the dome of the bladder in 6 patients, above the trigone in 4 and within a large diverticulum in the remaining patient.

Pre-operative tumour staging and screening for metastatic disease included cystoscopy, bimanual examination and biopsy, biochemical liver profile, chest X-ray and bone scan. Pre-operative bowel preparation and antibiotics were standard in all patients.

Operative technique

The patients underwent 1 of 2 surgical techniques according to the surgeon's preference.

Read at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

Table 1 Distribution of Tumours

	Male	Female	Total	Mean age (years)
Transitional cell carcinoma	8	3	11	55
Adenocarcinoma	2	1	3	37
Squamous cell carcinoma	2	0	2	33
Small cell carcinoma	1	0	1	43
Total	13	4	17	49

Group 1. The hemi-Kock ileocystoplasty. Following complete or subtotal cystectomy, depending on the site of the tumour, the neobladder was constructed from a length of terminal ileum. The operation was adapted to create a subtotal supratrigonal cystoplasty or a total bladder replacement, maintaining the urethral outlet. The technique of the hemi-Kock, non-refluxing ileocystoplasty was described by Weinberg *et al.* (1988) as an augmentation and Skinner *et al.* (1989) as a continent urinary diversion. A 60-cm length of terminal ileum is isolated on a mesentery and all except 17 cm, which form the afferent limb, is detubularised and fashioned by an S or W configuration into a planar segment (Fig. 1). The non-refluxing valve is created from the intact ileum by separating 8 cm of the mesentery of the bowel wall adjacent to the neobladder, which facilitates intussusception and prevents subsequent slippage. The nipple valve is held by 3 rows of staples using a TA 55 device; this

includes a row that fixes the nipple to the ileal wall. The ureters are anastomosed to the proximal end of the afferent limb using the standard Wallace technique. The distal neobladder is then anastomosed to the urethra or bladder remnant.

Group 2. Detubularised ileocaecal cystoplasty. Following cystectomy, the terminal ileum, caecum and ascending colon are mobilised and the appendix removed. The cystoplasty segment is isolated on the ileocaecal artery and then intestinal continuity is restored with a 2-layered anastomosis. The terminal ileum is closed in 2 layers and the ileocaecal segment detubularised. The planar ileocaecal segment is then fashioned into a pouch and anastomosed to the urethra or bladder remnant. The ureters are implanted in an anti-reflux manner in 4-cm tunnels using the Leadbetter-Politano technique (Leadbetter, 1951).

Results

Follow-up ranged from 2 to 52 months (mean 26). During this time there were 4 deaths from widespread metastatic disease. Two of these patients had transitional cell carcinoma, 1 adenocarcinoma and the remaining patient had small cell carcinoma. A number of factors have been reviewed during follow-up.

Continence. Day time continence was achieved in all patients except one. Nocturnal enuresis occurred occasionally in a further 6 patients. Voiding *per urethram* was achieved by abdominal straining with simultaneous relaxation of the pelvic floor (Fig. 2). Three patients were unable to void completely and required intermittent clean self-catheterisation (ICSC).

Urodynamic assessment, which was performed on 5 patients, confirmed that these 2 operative techniques provided a low pressure reservoir of adequate volume with no evidence of significant high pressure contractions (Table 2).

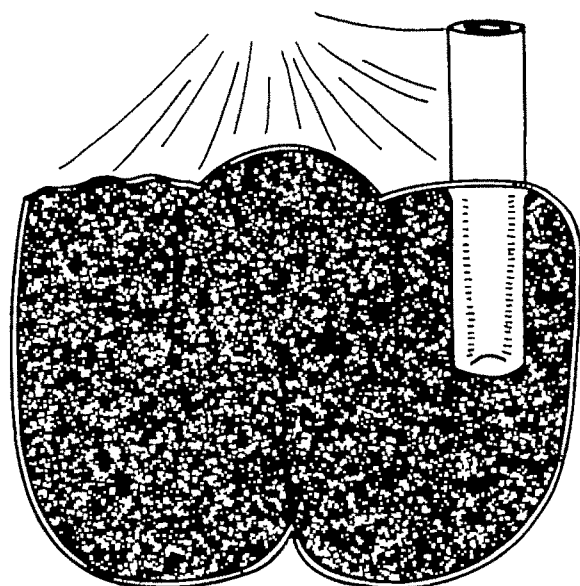
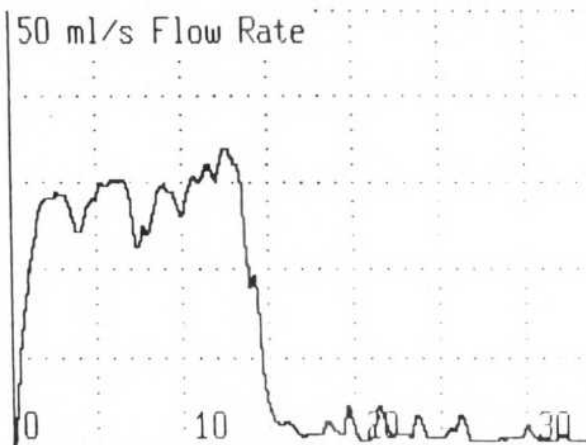


Fig. 1 Detubularised ileum in a W configuration also demonstrating the intussuscepted nipple valve.



Voided volume 435 ml

Residual urine 50 ml

Fig. 2 Voiding flowmetry demonstrating a peak flow of 32 ml/s and satisfactory emptying in a patient with an ileocystoplasty.

Urinary infection. During follow-up 4 patients developed symptomatic urinary infection requiring treatment; 2 with a large residual volume proceeded to ICSC. A further 4 patients showed asymptomatic bacteriuria, the significance of which is unclear. No patient developed ascending urinary infection and intravenous urography showed normal upper tracts in all patients, demonstrating competence of the anti-reflux mechanism (Figs 3 and 4).

Potency. Potency was assessed by uncorroborated post-operative questioning and 7 of the 11 male patients claimed maintenance of erections sufficiently rigid for intercourse.

Stones. Two patients formed small bladder stones which passed spontaneously, although 1 required endoscopic removal of a stone which became lodged in the urethra. One of these was also found to be hypercalciuric. To date no patient has developed stones on the metal staples of the intussuscepted nipple.

Table 2 Urodynamic Findings of Cystoplasties

	Mean	Range
Residual volume (ml)	110	0–300
Maximum filling pressure (cm H ₂ O)	20	8–29
Bladder capacity (ml)	580	210–980



Fig. 3 Intravenous urogram of patient in Figure 1 showing normal upper tracts draining into the non-refluxing afferent limb of ileum.



Fig. 4 Cystogram phase of the same urogram showing neo-bladder and afferent limb.

Mucus production. Mucus production was an immediate post-operative problem in 2 patients and although they continue to pass mucus it has not since been of any clinical significance.

Electrolyte disturbance. Minor electrolyte disturbance is inevitable after cystoplasty but was not a clinical problem in any of the patients, probably because of the young age of the group.

Discussion

A clear strategy for the treatment of urothelial neoplasia has been obscured by the long natural history of the disease and the uncertainty of the significance of various prognostic indicators. The relationship between grade, muscle invasion and survival was established at an early stage (Wallace, 1959); more recently, Skinner and Lieskovski (1988) suggested that the critical depth of penetration is the perivesical fat. The correct treatment of each of these stages of tumour, however, remains unclear.

Early studies comparing surgery alone with the combination of pre-operative radiotherapy and surgery were inconclusive. Whitmore *et al.* (1968) suggested a significant improvement in survival in the combination group but Prout *et al.* (1971) and Skinner and Lieskovski (1984) failed to confirm this advantage. The latter authors suggested that the improved peri-operative care of patients today was responsible for the improved survival of those treated by operation.

Large studies from Bloom *et al.* (1982) and Blandy *et al.* (1980) have shown the value of radiotherapy alone, especially in patients over the age of 65 years and in those who show a good response to treatment. These results, combined with the desire of both patients and surgeons to avoid the creation of an incontinent abdominal stoma, have led to most centres performing salvage cystectomy only in cases of tumour recurrence or non-response to EBRT.

EBRT itself is not without adverse effects, with serious gastrointestinal complications occurring in up to 6% of those treated (Smalley and Evans, 1991). When proceeding with cystectomy after EBRT, significant complications can occur in up to 34% of patients (Yu *et al.*, 1985). Combined with the attendant psychosocial implications (Mansson *et al.*, 1988) and decreased sexual capacity that follow radical non-nerve-sparing cystectomy, the potential of reconstructive procedures in the treatment of bladder cancer has become attractive. Initial results in the United States (Reddy *et al.*,

1987; Ahlering *et al.*, 1991) have been encouraging, though experience in the UK is limited.

The results in this series compare favourably with the experience of others. The substituted bladders provide a low pressure reservoir that can be easily emptied, remains continent and preserves upper tract function. Not all of our patients had such an ideal result but all were pleased with the avoidance of a stoma and/or the preservation of potency. Local disease recurrence has not yet been a problem but longer-term follow-up will determine whether the urothelial remnants in these patients are a source of further neoplastic development. Intestinal mucosa itself within the urinary tract is also at risk of malignant transformation. It is our policy to perform flexible cystoscopy regularly on all patients. The risk of developing tumour recurrence in the urethral remnant appears to be small. A review of 200 cases of radical cystectomy by Levinson *et al.* (1990) showed the risk to be slight (1.5%) if the tumour was solitary and away from the prostatic urethra. Pathological studies have shown that urethral tumours occur half as often with single, solid tumours than with multiple papillary growths (Hendry *et al.*, 1974).

Four patients in the present series have died of distant metastatic disease during an overall mean follow-up of 26 months. These mortality rates are comparable to those expected for T3 tumours, which have a median survival of 2 years and a 5-year survival rate of approximately 30% (Shearer *et al.*, 1988). One of the patients who died had a small cell carcinoma, which carries a particularly poor prognosis (Mills *et al.*, 1987), especially as there were positive lymph nodes at the time of surgery. Cystoplasty was performed, despite the poor prognosis, at the patient's request and he remained potent and continent until his death.

The perceived benefits of these operations to the patient are the avoidance of a stoma and the preservation of potency. Cystectomy was performed with preservation of the neurovascular bundle wherever possible, and this allowed for continent micturition and maintenance of erections (Schlegel and Walsh, 1987). The post-operative potency rate of 64% is similar to that achieved in other series (Marshall *et al.*, 1991) and is of particular relevance when taking account of the age of the men in this series. Continence was achieved in all but 1 patient, who had an ileocolic segment cystoplasty, though a further 6 patients had occasional episodes of nocturnal enuresis. The neobladders are large volume, low pressure reservoirs and voiding is assisted by performing the

Valsalva manoeuvre. Those patients who were unable to void completely, in particular those who developed residual volumes >200 ml, were managed by ICSC. The satisfactory level of continence achieved is a reflection of the technical success of the cystoplasty and again the young age of the patients.

Although cystectomy and bladder reconstruction are not suitable for all patients with T2/3 bladder carcinoma, encouraging developments with neoadjuvant chemotherapy (Herr *et al.*, 1990) may enable reconstructive procedures to become available to more patients than those selected in this series. A recent controlled trial suggested improved disease-free intervals and survival rates for patients receiving adjuvant post-operative chemotherapy (Skinner *et al.*, 1991). Cystoplasty and adjuvant chemotherapy may yet prove to be a therapeutic alternative to EBRT and cystectomy.

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Age-related Variation in Urinary Flow Variables and Flow Curve Patterns in Elderly Males

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Summary—A group of randomly selected males, over 50 years of age, was examined with regard to history and urinary flow rate. Originally, the group had comprised 93 men without voiding problems, 15 who, although suffering from voiding problems, had not yet contacted their doctor, and 4 who had contacted their doctor because of voiding problems. Five years later the data were re-examined and 61 men were fully investigated again; in the remaining 51 patients only the history was updated. The 2 sets of data were evaluated separately as 2 cross-sectional investigations and as paired data sets by means of non-parametric statistical analysis.

All uroflow variables were considered, *i.e.* Q_{max} , Q_{ave} , Q_{max} -time, Q "corrected", volume and the ratio Q_{max}/Q_{max} -time. In addition, the flow curve configuration was classified as normal or abnormal.

When compared as 2 cross-sectional investigations, the latter confirmed the results of the first. Q_{max} , Q_{ave} , Q "corrected" and volume decreased with advancing age, but no correlation could be demonstrated between Q_{max} -time and age. The flow curve pattern altered, so that a normal flow curve was seldom seen at an advanced age. Uroflow variables tended towards the abnormal with advancing years and symptoms increased concurrently. These changes were largely accepted by the elderly males. Thus the decision to operate for benign prostatic hyperplasia should be based on both history and urinary flow.

The indications for prostatic resection are usually relative. Transurethral resection of the prostate (TURP) is most often performed to relieve symptoms and to prevent future morbidity. Thus a common problem confronting the urologist is to decide when and to whom surgical treatment should be offered for benign prostatic hyperplasia (BPH). For some time it was thought that the patient's history was too unreliable to form the basis for decision-making and much importance was placed on the results of urodynamic investigations. It is now widely accepted that in patients with relative indications for operation, both symptoms and urodynamics must be considered. Since full urodynamic investigation requires both personnel and time, and these are not always available in all clinics, it may be necessary to rely on history and urinary flow alone in the pre-operative period and

as much data as possible should be extracted from these investigations. At the same time one must be able to discriminate between normal and abnormal data. Many studies have been made of micturition patterns (Frimodt-Møller, 1974; Gammelgaard, 1974; Anikwe, 1976; Andersen *et al.*, 1978; Drach *et al.*, 1979; Siroky *et al.*, 1979, 1980; Ryall and Marshall, 1982; Jensen *et al.*, 1983; Tripathi and Sridhar, 1983) but in general they were small or based on populations where BPH was seldom seen. The natural course of mild, subjectively insignificant BPH has not been reported. We have therefore tried to provide an age-related study and to describe the spontaneous course of BPH over a 5-year period.

Patients and Methods

All procedures and definitions are in accordance with the proposals of the International Continence Society (Abrams *et al.*, 1988) except where noted.

A random sample of 200 males, aged 50 years or more, was selected from the National Register. The sample matched the male population of the metropolitan area with regard to age.

Forty-three subjects did not respond to our letters; 22 were either unable or unwilling to participate; 3 died prior to investigation and 10 were either hospitalised, chronically ill or in nursing homes. Prostatectomy had been performed in 6 patients and 4 were excluded because of bladder tumours, insulin-dependent diabetes and the sequelae of stroke. Thus 112 men were studied (median age 64.5 years, range 50–90). Nineteen had subjective voiding problems but none had undergone surgery on the bladder, prostate, urethra or rectum. None of the participants used medication capable of influencing the voiding process or suffered from neurological disease, diabetes mellitus, haematuria or urological cancer.

A symptom score was calculated according to Jensen *et al.* (1986). Obstructive and irritative symptoms were graded equally, the maximum score in each category being 10 points.

Using the DISA mictograph 14F43, voiding was recorded in all 112 males. To ensure optimal voiding conditions and reproducible data (Heinz and Hallwachs, 1982; Jensen *et al.*, 1985), the subjects voided in the afternoon, in privacy and in the standing position when the desire to void was felt. The mictograph was tested by means of 3 standard flow rates of 8, 12.5 and 20.5 ml/s and the voided volumes were measured using calibrated glasses.

From the flow curve Q_{max}, Q_{max}-time and flow time were read. Voiding was considered to have been initiated when the flow exceeded 2 ml/s and we did not consider any deviations from the zero lines of less than 2 ml/s at the end of voiding (Gleason *et al.*, 1967).

The type of flow curve was defined according to Jørgensen *et al.* (1990). Type 1: unbroken and bell-shaped with only slight to moderate asymmetry of the "bell". Type 2: unbroken with pronounced asymmetry and an elongated, flattened course from Q_{max} to zero. Type 3: unbroken, but characterised by greater fluctuations without reaching zero before the end of the voiding procedure. Type 4: discontinuous, characterised by one or several episodes where the flow was zero. Type 5: unbroken, flattened and a large part of the voided volume was voided by a constant Q_{max}.

Q_{ave} was estimated from the data and the volume-independent Q_{corrected} was calculated from Q_{max}/square root of the voided volume (Siroky *et al.*, 1979). The ratio Q_{max}/Q_{max}time

Points	0	1	2	3	4
Stream	Normal	Variable		Weak	Dribbling
Hesitancy	None		Yes		
Intermittency	None		Yes		
Incontinence (non-urge)	None		Yes (incl terminal dribbling)		
Urge	None	Mild (not often)	Moderate (every day)	Incont	
Nocturia	0–1		2	3–4	>4
Voiding interval (h)	>3	2–3	1–2	<1	

Fig. 1 Symptom score. Maximum score is 10 for both irritative and obstructive symptoms.

was calculated to describe the "acceleration" to Q_{max}.

All participants were asked whether they considered the voiding to have been normal or abnormal. They were also asked about symptoms of prostatism (Fig. 1).

After a period of 4.5 to 5 years all data were evaluated. Of the initial 112 males 17 had died, 8 had undergone treatment for BPH, 1 was excluded with malignant neoplasm of the bladder, 1 was excluded because of total incontinence following a stroke, 11 were chronically ill either at home, in hospital or in nursing homes, 5 had moved elsewhere and 8 no longer wished to participate. Thus 61 males were left for further urodynamic study (median age 71.9 years, range 55–88). All of the procedures used initially were repeated using the same equipment (calibrated with the same standard flows) and the sampled data are presented both graphically and by means of non-parametric statistical analysis. Throughout the study *P* values less than 0.05 were considered significant. The initial data have been presented by Jørgensen *et al.* (1986) and Jensen *et al.* (1986).

Results

The age distribution from 1984 to the present is summarised in Figure 2 and reflected the selection

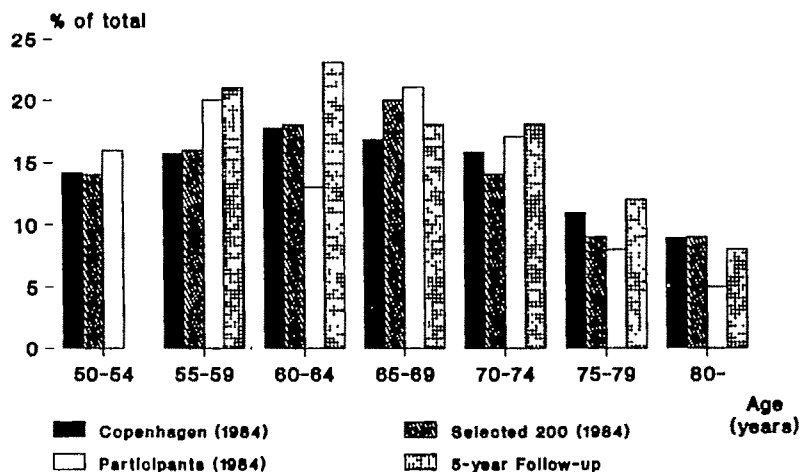


Fig. 2 Age distribution in males over the age of 49 years. Percentage of total is given.

procedure, *i.e.* the sample of 200 males shows the same age distribution as the males in the metropolitan area. The selection at entry to the study in 1984 did not alter the picture, but at follow-up the effect of natural selection was seen, *i.e.* some men had died, were chronically ill or had been treated for prostatism. The 8 males who received treatment for prostatism might have affected the results of the evaluation of uroflow variables but this was not the case in any of the flow variables under consideration. To illustrate this problem the $Q_{\max}$ versus age and volume versus age relations are shown as examples in Figure 3. For each flow variable the treated males were scattered randomly throughout the population. The degree of prostatism in the treated and untreated group did not differ significantly, as the median total symptom score in the whole group was 4 points (range 0–16) versus 6 points (range 2–10) in the treated group. The uroflow variables from the 5-year follow-up were evaluated separately as a cross-sectional investigation. Correlation with age was estimated by means of the Spearman test. The results are shown in Table 1 and when these are compared with the results obtained 5 years previously, a significant decrease in $Q_{\max}$, $Q_{\text{corrected}}$ and voided volume with advancing age becomes evident. No correlation was found between $Q_{\max}$ -time and age, whereas the "acceleration" from the initiation of voiding to $Q_{\max}$ diminished significantly with advancing age.

The flow curves were classified according to the definitions already mentioned. The data were allocated to 2 groups: normal (type 1) and abnormal (types 2–5). A statistically significant correlation

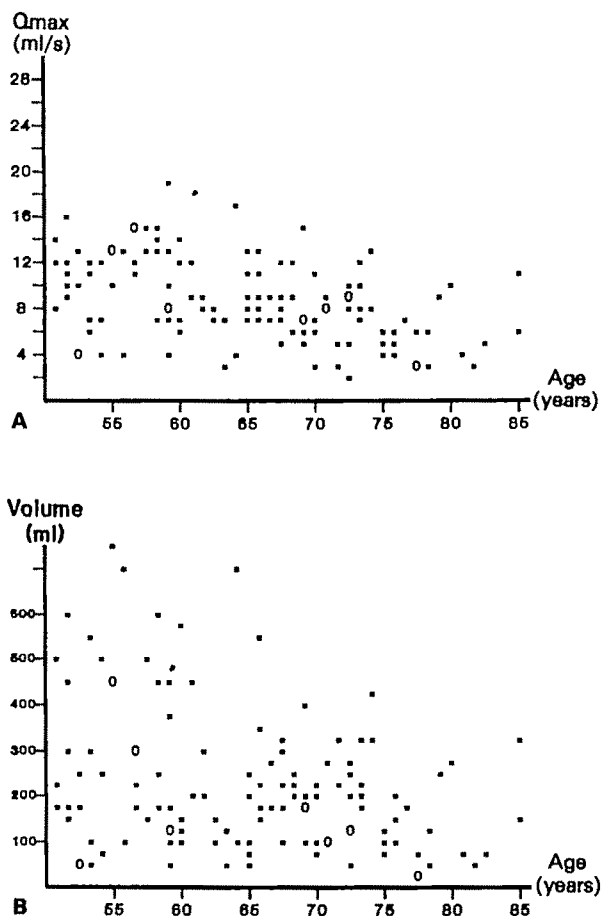


Fig. 3 (A) $Q_{\max}$ values at entry to the study. ■ = not treated at 5-year follow-up. ○ = treated at follow-up. (B) Voided volumes at entry to the study. ■ = not treated at 5-year follow-up. ○ = treated at follow-up.

Table 1 Correlation between Age, Uroflow Variables and Symptom Scores at Initial Investigation and 5-year Follow-up (Spearman test, 2-tailed)

Age versus	Initial examination	5-year follow-up
Qmax	$P < 0.001$	$P < 0.001$
Qave	$P < 0.001$	$P < 0.001$
Q"corrected"	$P < 0.001$	$P < 0.005$
Volume	$P < 0.01$	$0.01 < P < 0.05$
Qmax-time	$0.2 < P < 0.3$	$0.2 < P < 0.4$
Qmax/Qmax-time	$0.04 < P < 0.05$	$P < 0.01$
Symptom score	$P < 0.01$	$P < 0.001$

was found between flow curve type and age, a normal flow curve being unusual at an advanced age (Figs 4 and 5).

In Table 2 the data from the initial examination and the follow-up were pooled in order to perform the Wilcoxon-Pratt test for paired data. The alterations within the test group are reflected, *i.e.* the Qmax-related data show the same decline with advancing age, but the data from the follow-up are displaced to a higher, equidistant level compared with the initial data. To illustrate this finding, some of the age-related data from the 2 tests are presented

75% percentile

50% percentile
(median)

25% percentile

Range

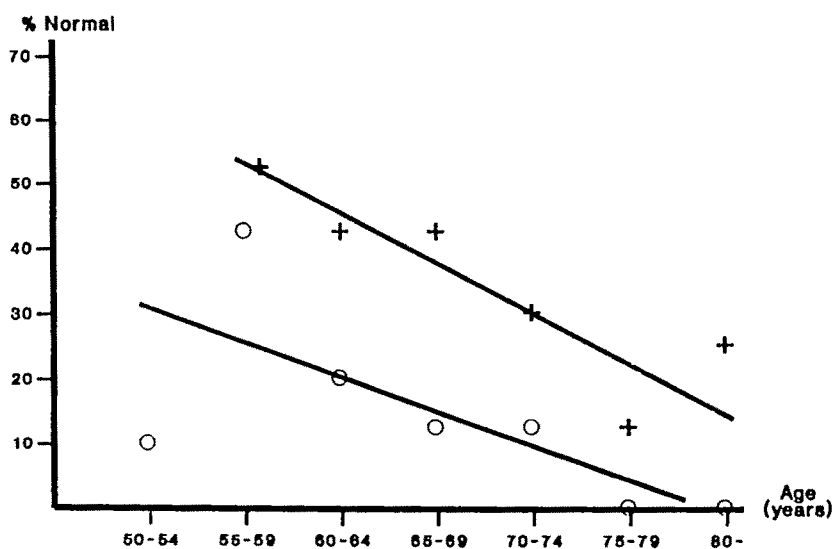
**Fig. 4** Key to the graphs**Fig. 5** Relation between flow curve type and age. Percentage of normal flow curve types is given. ○ = initial investigation. + = 5-year follow-up

Table 2 Comparison of Uroflow Data from Initial Investigation and 5-year Follow-up (Paired observations, Wilcoxon/Pratt test)

Qmax	$P < 0.01$
Qave	$0.1 < P < 0.2$
Q"corrected"	$P < 0.001$
Volume	$0.1 < P < 0.2$
Qmax-time	$0.01 < P < 0.02$
Qmax/Qmax-time	$P < 0.001$
Symptomscore	$0.03 < P < 0.05$

graphically in Figures 6, 7 and 8. The subjects were divided into 5-year groups and range, 25%, 50% (median) and 75% percentiles used to describe each age group. The symptom score/age relation was examined in the same manner, showing significant correlation both at the initial examination and at 5-year follow-up. The 2 sets of data did not differ when compared as paired observations.

Based on the pooled data, nomograms for Qmax, voided volume and "acceleration" and their relation to age were constructed using 2.5%, 50% and 97.5% percentiles (Figs 9, 10 and 11).

Discussion

The aim of the present study was to describe changes in uroflow variables in a test group of elderly males. The reduction of the group to half of its original size over a 5-year period does not

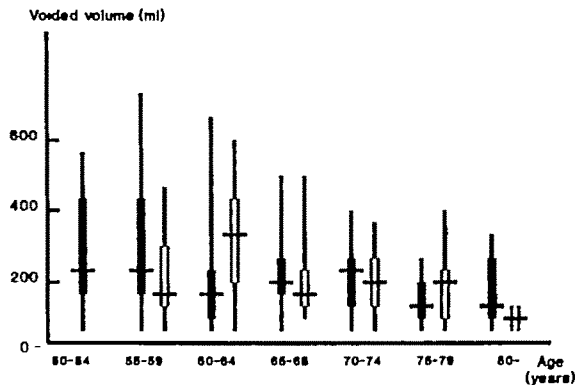


Fig. 7 Relation between voided volume and age. Values in each age group are presented as explained in Figure 4, giving range values and 25%, 50% (median value) and 75% percentiles. Full graphs represent initial data. Open graphs represent data from 5-year follow-up.

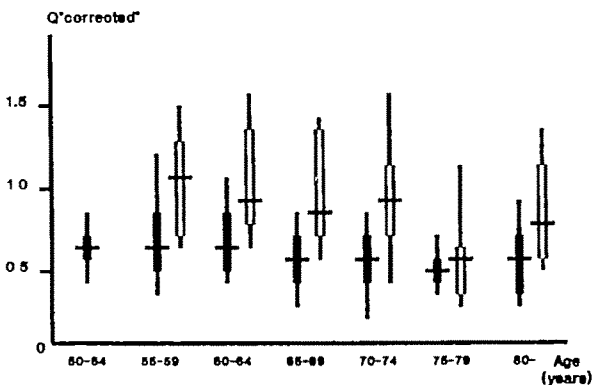


Fig. 8 Relation between "corrected" Qmax and age. Values in each age group are presented as explained in Figure 4, giving range values and 25%, 50% (median value) and 75% percentiles. Full graphs represent initial data. Open graphs represent data from 5-year follow-up.

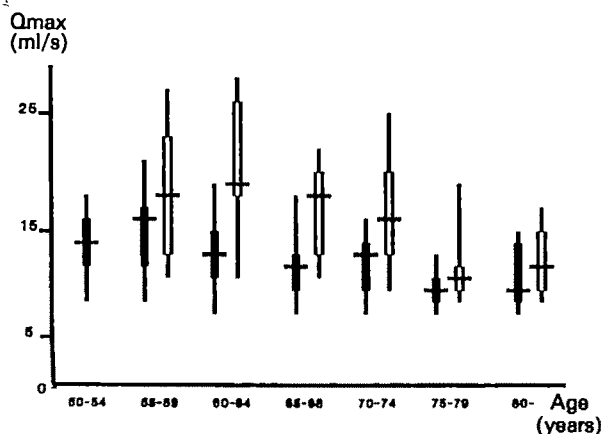


Fig. 6 Relation between Qmax and age. Values in each age group are presented as explained in Figure 4, giving range values and 25%, 50% (median value) and 75% percentiles. Full graphs represent initial data. Open graphs represent data from 5-year follow-up.

conflict with the aim, since the last decades of life are characterised by natural morbidity and mortality.

Eight men underwent treatment for BPH before follow-up. As has been demonstrated, primary uroflowmetry could not have picked them out as being a significantly different subgroup. In addition, symptom analysis revealed that their scores were within the 25% and the 75% percentiles of the test group, and that the scores were obtained on irritative and obstructive symptoms equally. It is not clear why these particular men required surgery.

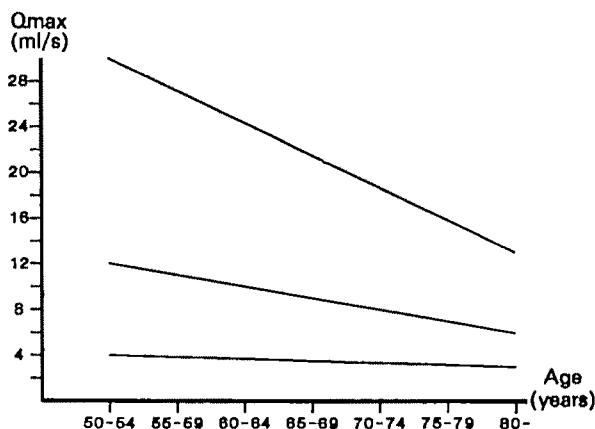


Fig. 9 Relation between Qmax and age. Nomogram based on pooled data, 2.5%, 50% (median) and 97.5% percentiles are given

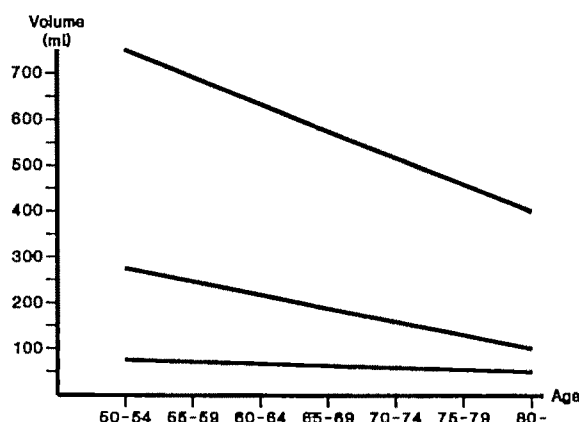


Fig. 10 Relation between voided volume and age. Nomogram based on pooled data; 2.5%, 50% (median) and 97.5% percentiles are given.

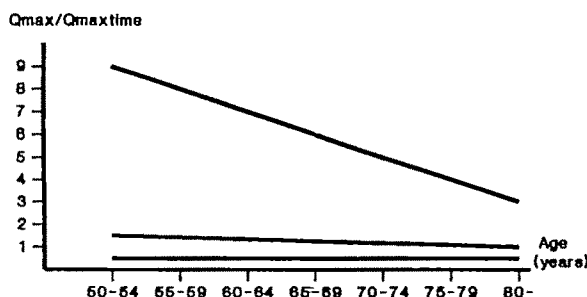


Fig. 11 Relation between "acceleration" and age. Nomogram based on pooled data ("acceleration" explained as Qmax divided by Qmax-time), 2.5%, 50% (median) and 97.5% percentiles are given.

Both the initial investigation and the follow-up show, as cross-sectional investigations, that Qmax and uroflow variables derived from Qmax decline with advancing age. It is, however, surprising that the values from the follow-up study decline from a higher level, i.e. the values from the follow-up are equidistantly displaced to higher levels compared with the corresponding initial data. As the voided volumes showed very little variation over the 5-year period, one might explain the differences in uroflow variables as artifacts on the basis of calibration faults. However, the uroflows were measured on the same mictiograph on both occasions and the mictiograph was calibrated prior to each investigation using the same standard flows. Even the standard flows were tested for accuracy and all tests and calibration procedures were carried out by the same person. Some variation may have arisen from the natural selection as the study group had decreased from 112 to 61 subjects, but the exclusion of the 8 men treated for prostatism did not affect the overall picture. Also, the "learning effect" described by Dutarte and Susset (1974) may provide a partial explanation. Finally, a cyclic intra-person variation in the "bladder neck obstruction/detrusor power relation" may have affected the results, but the existence of this cyclic variation has not been proven.

The 2 studies show that Qmax, "corrected" Qmax, voided volume and acceleration decline with advancing age. At the same time the flow curve pattern shifts from normal to abnormal and symptom scores increase. Half of the men had Qmax < 15 ml/s and one-third had Qmax < 10 ml/s. Half of them had a voided volume < 200 ml and one-third a voided volume < 150 ml; 40 to 50% of the flow curves were normal at the age of 50 years, whereas only 10% were normal by 80 years.

In conclusion, uroflow variables reveal a considerable degree of infravesical obstruction/detrusor insufficiency at an advanced age, but neither symptoms of prostatism nor a urodynamic demonstration of infravesical obstruction alone indicate the need for surgery.

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Urinary Flow Rate in Benign Prostatic Hypertrophy in Relation to the Degree of Obstruction of the Vesical Outlet

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Summary—Forty men with bladder outflow obstruction from benign prostatic hypertrophy were investigated urodynamically by medium-fill water cystometry and pressure flow study. The most obstructed patients proved to be unstable. A positive link was found between the degree of obstruction, as assessed by the opening pressure (*i.e.* the detrusor pressure needed to start micturition), and the maximum mechanical power generated by the contracting bladder during voiding. What seems most striking, is that neither detrusor contraction velocity nor the urine flow rate fully mirrored the degree of obstruction—*i.e.* the opening pressure and the maximum contraction speed did not show a negative correlation, but rather a weak (though insignificant) positive link, and the flow rate decreased only slightly (not significantly) when obstruction increased. Such a surprising observation could be explained by the fact that prostatic obstruction produces both collagen infiltration into the bladder muscle (this affecting the spread of the depolarisation wave) and, at the same time, denervation supersensitivity. The latter actually yields a decrease in electrical resistance between the detrusor smooth muscle cells (and thereby an enhanced synchronisation of the detrusor contraction), which might be only partly cancelled by the effects of collagenosis.

A negative correlation would be expected to exist in benign prostatic hypertrophy (BPH) between the degree of obstruction of the vesical outlet on the one hand and the shortening velocity of the contracting detrusor, as well as the urinary flow rate, on the other. Recent investigations suggest this is not always the case, however, (Griffiths *et al.*, 1989; Cucchi, 1990), and such impressions are further confirmed herein. A series of speculations may be derived from the results of the present paper, which are now offered in an attempt to clarify these matters.

Patients and Methods

In 1989 and 1990 a large number of patients with both obstructive and irritative symptoms of mictu-

rition from BPH were referred to our unit for urodynamic assessment of bladder outflow obstruction (BOO). The investigation comprised spontaneous free flow uroflowmetry and medium-fill water cystometry with pressure flow study. Cystometry was performed by infusing 0.9% saline at room temperature through a 10F Nélaton transurethral catheter with the patient upright. Abdominal pressure (p_{abd}) was recorded through a 16F rectal balloon catheter inflated with 10 ml saline, and detrusor pressure (p_{det}) was calculated by electronically subtracting p_{abd} from the intravesical pressure (p_{ves}), as measured through an 8F Nélaton transurethral catheter. Both pressure-measuring catheters were connected through fluid-filled lines to external strain gauge transducers mounted on a stand at the level of the patient's symphysis pubis.

During filling, care was taken to note detrusor instability (DI), as defined according to the International Continence Society (Abrams *et al.*, 1988).

At maximum cystometric capacity (MCC) the 10F catheter was removed and a pressure flow study was done with the patient upright. Urine flow rate was measured by a weight flowmeter. Detrusor and abdominal pressures and the urine flow rate were recorded on a paper strip chart recorder. Computer analysis of the urodynamic data was also performed. The pressure flow values, along with the isometric pressure rise before flow started, were digitised by direct online data acquisition and subsequently analysed by a computer program. Synchronisation of the pressure flow signals was done with a correction of 0.7 s for the delay in flow rate measurement.

Patients being treated with drugs that may interfere with detrusor function were excluded from the study, along with those who, in addition to BPH, had urethral strictures, bladder stones or neoplasms, neurological, metabolic, or mental diseases, or any other disturbances that could directly or indirectly affect bladder filling or voiding.

BOO was defined first on the basis of pressure flow study as a peak flow pressure ($p_{\text{det } Q_{\text{max}}}$) of $>75 \text{ cmH}_2\text{O}$, with a maximum flow rate (Q_{max}), at spontaneous free flow uroflowmetry, of $<12 \text{ ml/s}$ for patients aged from 46 to 55 years, or $<9 \text{ ml/s}$ for patients aged 56 years or more (Abrams, 1984). Patients whose maximum flow rates were higher than 9 or 12 ml/s (or even higher than 15 ml/s) have been considered as obstructed if showing a maximum detrusor pressure ($p_{\text{det } \text{max}}$) of $>100 \text{ cmH}_2\text{O}$ (Smith, 1968). Furthermore, the diagnosis of BOO was confirmed in all subjects by visual inspection of an x-y plot of detrusor pressure against flow rate throughout micturition (Abrams and Griffiths, 1979).

The degree of obstruction was assessed by the opening pressure ($p_{\text{det } \text{op}}$), this being assumed (after the aforementioned correction for the time delay in the measurement) as a reasonable approximation to the minimum static pressure (p_{muo}) necessary in the proximal urethra to start (and to maintain) the urinary flow (Schaefer *et al.*, 1988). In the case of pseudodyssynergic voiding patterns, *i.e.* when $p_{\text{det } \text{op}}$ was higher than the pressure at the end of flow or even at peak flow (owing to delayed relaxation of the bladder outlet), the pressure flow study was repeated after inviting the patient to relax fully before starting micturition. This resulted in synergic voidings in all cases, and insignificant differences were found between $p_{\text{det } \text{op}}$ and the pressure at the end of flow—which further enables us to regard $p_{\text{det } \text{op}}$ as reasonably approximating to p_{muo} . Finally, it

must be noted that minimal differences in $p_{\text{det } \text{op}}$ were found when evaluating more than 1 (synergic) voiding in the same patient.

From those with BOO who fulfilled the requirements needed to enter the study, 40 patients (mean age 65 ± 9 years)—20 with stable bladders (Group A) and 20 with DI (Group B)—were chosen at random. For each of these subjects the following parameters were recorded from pressure flow study: MCC (ml), $p_{\text{det } \text{op}}$ (cmH_2O), $p_{\text{det } Q_{\text{max}}}$ (cmH_2O), $p_{\text{det } \text{max}}$ (cmH_2O), Q_{max} (ml/s), and, in addition: the “corrected” maximum flow rate (cQ_{max} (s^{-1})), *i.e.* Q_{max} divided by the square root of MCC, which is a volume-independent measure of Q_{max} (von Garrelts, 1957); the average flow rate (Q_{ave} (ml/s)), *i.e.* voided volume divided by flow time.

Finally, the parameters w_{max} and dl/dt_{40} were determined in each patient in order to represent the strength and velocity, respectively, of voiding contractions. The index w_{max} ($\mu\text{W}/\text{mm}^2$) equals the maximum mechanical power per unit of bladder wall surface area generated by the contracting detrusor. The commonest way of assessing the strength of micturition contractions is actually to calculate the external mechanical power developed (*i.e.* detrusor pressure $\times$ flow rate), but this depends on the volume in the bladder and is not constant for a constant contraction strength, tending to decrease for decreasing flow rate or decreasing pressure. The parameter w_{max} (Griffiths *et al.*, 1986) is in a modified form in which such problems are overcome, so it can be assumed as a useful index of contractility (van Mastrigt, 1990). This equals the maximum of a variable (WF) that can be calculated throughout micturition,

$$WF = [(p_{\text{det}} + a)(v + b) - ab]/2\pi,$$

where a and b are constants ($25 \text{ cmH}_2\text{O}$ and 6 mm/s , respectively) and v derives from an equation (Griffiths *et al.*, 1986) in which the bladder is treated as spherical in shape.

The index dl/dt_{40} (mm/s) equals the shortening velocity of the contracting detrusor at 40 ml before the end of micturition. This was taken, according to Rollema and Griffiths (1984), as a close approximation to the maximum contraction speed (which is normally achieved just near the end of voiding), and was calculated (Rollema *et al.*, 1977) as $CQ/3V^{2/3}$, which assumes treating the bladder as a thin-walled sphere, with C being a constant and Q and V the flow rate and the volume in the bladder, respectively.

In all cases the urine flow proved continuous and ended synchronously with micturition contraction.

For each subject more than 1 voiding cycle was recorded, and for each parameter the median of individual values recorded during different examinations was considered for analysis.

Methods, definitions and units conformed to the standards proposed by the International Continence Society (Abrams *et al.*, 1988) except when specifically noted.

Medians and ranges of the parameters MCC, $p_{\text{det op}}$, $p_{\text{det Qmax}}$, $p_{\text{det max}}$, Q_{max} , cQ_{max} , Q_{ave} , w_{max} and dl/dt_{40} , as derived from pressure flow study, are shown in the Table for both Groups A and B, differences being checked for significance by Wilcoxon's rank sum test. The same test was used to check for the significance of differences in the patients' ages as well as in the fraction of bladder volume voided (VV%), this being calculated as volume voided $\times 100/\text{MCC}$ and assumed as an index of voiding efficiency.

The parameter $p_{\text{det op}}$ was plotted against w_{max} (Fig. 1), dl/dt_{40} (Fig. 2), Q_{max} (Fig. 3), cQ_{max} and Q_{ave} , correlation analysis being performed by Spearman's rho test.

Detrusor trabeculation has been assessed cystoscopically on an arbitrary 3-point scale (*i.e.* mild, moderate, or severe) according to the concept of Gosling and Dixon (1983) that the more trabeculated the bladder the higher the degree of detrusor collagenosis.

Table Medians, Ranges and Significance Levels of Difference by Wilcoxon's Rank Sum Test for Various Urodynamic (Pressure Flow) Parameters in 40 men with Prostatic Obstruction—20 Stable (Group A) and 20 Unstable (Group B)

	Group A	Group B	P
MCC (ml)	362 (205–782)	227 (200–363)	<0.001
$p_{\text{det op}}$ (cmH ₂ O)	77 (33–96)	97 (62–184)	<0.01
$p_{\text{det Qmax}}$ (cmH ₂ O)	89 (76–141)	107 (77–194)	<0.005
$p_{\text{det max}}$ (cmH ₂ O)	107 (79–144)	126 (89–223)	<0.005
Q_{max} (ml/s)	7.5 (3.0–15.0)	8.0 (3.0–23.0)	n.s.
cQ_{max} (s ⁻¹)	0.39 (0.19–0.75)	0.51 (0.21–1.30)	<0.05
Q_{ave} (ml/s)	2.5 (1.3–5.3)	2.9 (1.6–7.3)	n.s.
w_{max} ($\mu\text{W}/\text{mm}^2$)	14.5 (11–23)	19.5 (13–31)	<0.001
dl/dt_{40} (mm/s)	1.37 (0.25–6.46)	1.84 (0.53–17.67)	<0.025

Results

Patients' ages tended to be slightly (though not significantly) higher in the unstable Group B (median 69 years, range 50–80 years) than in the stable Group A (median 64 years, range 47–77 years).

The fraction of bladder volume voided (VV%) was higher ($P<0.05$) in Group B (median 100%, range 25–100%) than in Group A (median 70%, range 16–100%). No significant difference could be found between the 2 groups as regards both the maximum and the average flow rates as such, but Q_{max} proved higher in the unstable patients ($P<0.05$) when corrected for the MCC, in spite of the latter parameter being lower in Group A ($P<0.001$). The parameter dl/dt_{40} , too, was higher in the unstable males ($P<0.025$), and $p_{\text{det op}}$, $p_{\text{det Qmax}}$, $p_{\text{det max}}$ and w_{max} proved significantly higher in the same Group B.

The degree of obstruction of the vesical outlet, as assessed by $p_{\text{det op}}$, correlated significantly with w_{max} ($r_s=0.37$, $P<0.02$) (Fig. 1). No negative correla-

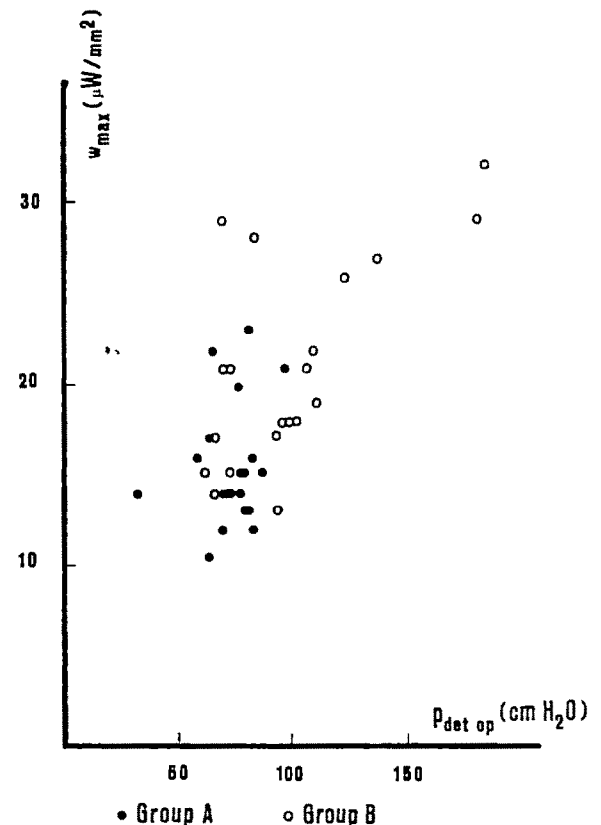


Fig. 1 Scatter plot of the opening pressure, $p_{\text{det op}}$ (assumed as an index of the degree of obstruction), versus maximum contraction strength, w_{max} . $r_s=0.37$ ($P<0.02$).

tion could be discovered between $p_{\text{det op}}$ and dl/dt_{40} . On the contrary, the 2 parameters showed a feeble (not significant) positive link ($r_s = 0.07$) (Fig. 2). Only a weak (not significant) negative correlation was found between $p_{\text{det op}}$ and Q_{max} ($r = -0.19$) (Fig. 3), cQ_{max} ($r_s = -0.16$) and Q_{ave} ($r_s = -0.17$).

Detrusor trabeculation proved rather marked (*i.e.* moderate to severe) in all cases.

Discussion

The following were observed.

- The greater the obstruction of the vesical outlet the higher the likelihood of DI—which confirms the results of previous studies (Cucchi, 1988, 1990).
- There is a positive correlation between the degree of obstruction, as assessed by the opening pressure ($p_{\text{det op}}$), and the maximum strength generated by the contracting detrusor (Fig. 1).

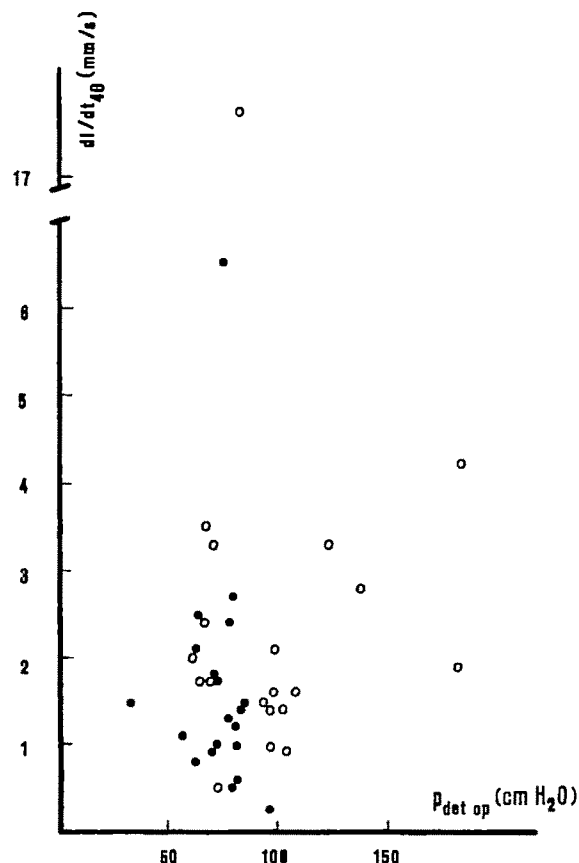


Fig. 2 Scatter plot of $p_{\text{det op}}$ versus maximum contraction velocity, dl/dt_{40} . $r_s = 0.07$ (n.s.)

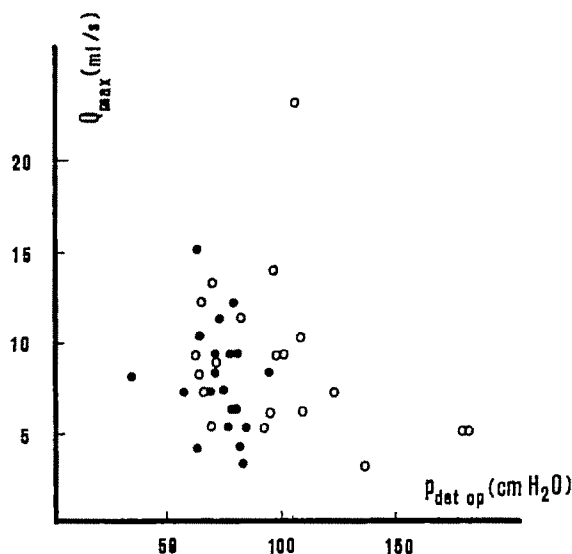


Fig. 3 Scatter plot of $p_{\text{det op}}$ versus maximum flow rate, Q_{max} . $r_s = -0.19$ (n.s.)

- What seems most striking, neither the contraction velocity nor the urinary flow rate fully mirrored the degree of obstruction—*i.e.* the opening pressure and the maximum contraction speed did not show a negative correlation, but rather a weak (though insignificant) positive link (Fig. 2), and the flow rate decreased only slightly (not significantly) when obstruction increased (Fig. 3).

The latter, surprising observation could perhaps be explained by the fact that BOO is a cause both of denervation supersensitivity (DS) (Speakman *et al.*, 1987) and, at the same time, of detrusor collagenosis (Ghoniem *et al.*, 1986). In effect, one has first to consider that DS involves important electrophysiological changes, namely (i) a decrease in the transmembrane potential of smooth muscle cells, and (ii) a decrease in electrical resistance between the same cells (Westfall, 1981). The former feature might be responsible for DI, and the latter for an easier electrical coupling—which, according to Westfall (1981), assumes (at least, in the animal model) an increased number of nexal contacts. (More recently, a highly suggestive association was found in humans by Elbadawi *et al.* (1990) between DI and the presence of “protrusion” cell junctions.)

Given the theory that obstructive DI is a DS phenomenon (Speakman *et al.*, 1986), one could infer from the observation labelled (a), above, that the greater the obstruction the higher is the likelihood of DS—presumably as a result of

increasing intravesical pressures causing damage to the detrusor autonomic innervation (Harrison *et al.*, 1987). Thus (at least from a theoretical viewpoint) it might even be derived from (ii) that increasing obstruction should result in an easier spread of the depolarisation wave throughout the bladder muscle, and thereby in enhanced synchronisation of the detrusor contraction, with increased values of contraction strength, contraction velocity, urinary flow rate and voiding efficiency.

On the other hand, it is known that increasing obstruction produces increasing infiltration of collagen tissue into the same bladder muscle (Ghoniem *et al.*, 1986). This obviously upsets the spread of the depolarisation wave, which is then forced through a pathway becoming more and more tortuous contingent upon the amount of connective fibres. Collagenosis seems to be rather heavy in the present series, according to the marked trabeculation which has been found cystoscopically. In spite of this, the effects of what would be a DS-related decrease in electrical resistance were not completely cancelled—at least, given the results mentioned in (c) above.

Better electrical coupling (perhaps due to an increased number of nexal contacts or to "protrusion" cell junctions) might cause the depolarisation wave to bypass many of the obstacles interposed by collagen fibres. This would prevent the contraction velocity from becoming too slow, and also most likely permit the same wave to spread over a greater number of smooth muscle cells than in obstructed bladders with collagen infiltration but with no or with minor DS. The latter feature, in particular, may account for increasing contraction strength with increasing obstruction, as indicated by (b) above. This compensates for reduced size and/or reduced distensibility of the bladder outlet—which, too, would tend to minimise the decrease in urinary flow rate when urethral resistance increases.

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Identification of Metastatic Disease by T Category, Gleason Score and Serum PSA Level in Patients with Carcinoma of the Prostate

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Summary—Pre-operative serum prostate specific antigen (Tandem-R assay), T category, Gleason score and the metastatic (M1) status of a consecutive series of 60 patients with newly diagnosed carcinoma of the prostate were studied prospectively. The results revealed that, of these variables, pre-operative serum PSA (> 100 ng/ml) was the single most important indicator of metastatic disease, with 100% predictive value. With this alone, 83.3% of M1 disease could be correctly identified. For the remaining 17%, however, we advocate a high index of suspicion if the tumour is T3–T4 category on digital rectal examination (predictive value = 71.4%) and has a high grade with a Gleason score 8–10 (predictive value = 81%).

The identification of metastatic (M1) disease in patients with carcinoma of the prostate has a significant prognostic value. It also influences the choice of treatment.

The UICC recommended T category to assess the local extent of the tumour (Wallace *et al.*, 1975). This is traditionally done by digital rectal examination (DRE) by urologists. Lymph node involvement (N category) is not easy to determine without resorting to node dissection surgery and thus is not routinely recorded. Prostate cancer spreads mostly to the axial and long bones and occasionally to the lungs and liver. Thus radiological investigation of these organs and radioisotope bone scans are used to determine the metastatic status (M0 or M1) of the tumour.

In order to quantify the grade of prostate cancer, Gleason (1966) reviewed the histological slides of VACURG trial patients and devised a scoring system. By virtue of its simplicity and reproducibility with less subjective variation, the Gleason sum score is widely accepted as a “gold standard” for prostate cancer grading (Benson and Olsson, 1989).

A high Gleason score correlates well with the death rate from cancer, yet the sum of clinical stage and Gleason score is prognostically more significant than either stage or grade alone (Sogani *et al.*, 1985). Even in incidental carcinoma of the prostate (T0), a high Gleason score is associated with metastasis at the time of diagnosis (Beynon *et al.*, 1983).

Serum prostatic acid phosphatase (PAP) and alkaline phosphatase were the only useful markers in prostate cancer until Wang *et al.* (1979) isolated a glycoprotein, prostate specific antigen (PSA). This is found in the cytoplasm of benign and malignant prostatic cells. It has a molecular weight of 34,000 daltons compared with 100,000 daltons for PAP, so that PSA can pass through the basement membrane and leak into the general circulation much earlier than PAP. PSA is more reliable than PAP in the diagnosis of prostate cancer because it is more sensitive, relatively more stable with time and temperature, and shows less diurnal variation (Brawer and Lange, 1989). Perhaps because of its historical value, serum PAP is still monitored routinely, together with PSA, in some centres. However, the overall clinical efficacy is higher with PSA and is no better when both markers are measured (Drago *et al.*, 1989; Morote-Robles *et al.*, 1989). In a review article, Shearer (1991) examined

the role of PSA in the diagnosis and management of prostatic cancer.

The purpose of the present study was to examine the efficiency of T category, Gleason score and serum PSA in order to identify metastatic disease in men with newly diagnosed carcinoma of the prostate.

Patients and Methods

A consecutive series of newly diagnosed patients with carcinoma of the prostate (CAP) between April 1989 and September 1990 was studied prospectively. There were 60 patients with an age range of 61 to 88 years (median 72). The T category was recorded by digital rectal examination under anaesthesia prior to transurethral resection (TUR) or at the time of transperineal biopsy of the tumour. The diagnosis of carcinoma of the prostate was confirmed by histological sections of TUR chips or needle biopsy specimens. The Gleason score was also provided by the same pathologist. Patients were divided into 3 groups depending upon their Gleason score, e.g. 2-4, 5-7 and 8-10. Blood samples were taken prior to DRE and serum PSA was measured by Tandem-R assay (normal range 0-4 ng/ml).

After the diagnosis of prostate cancer was confirmed, further investigations were carried out for metastatic disease. These included chest radiographs, isotopic bone scan, skeletal survey and tomography when indicated. Bone biopsy and marrow examination were seldom required. These data were analysed to examine the efficiency of T category, Gleason score and serum PSA in identifying the metastatic (M1) status of the tumour. Statistical analysis was performed with Student's *t* test.

Results

Of 60 patients in this study, 30 had M1 disease at presentation. Serum PSA was found to increase consistently with advancing T category in M1 disease but not in M0 disease (Fig. 1), the difference being highly significant ($P=0.0003$). Similarly, serum PSA increased with advancing Gleason score (Fig. 2). Within each range of Gleason scores, the rise in PSA was highly significant in M1 compared with M0 disease ($P=0.0019$ for Gleason score 5-7, $P=0.0051$ for score 8-10).

Tables 1 and 2 show the range of PSA in various T categories and Table 3 shows the range of PSA in various Gleason scores in M0 and M1 disease.

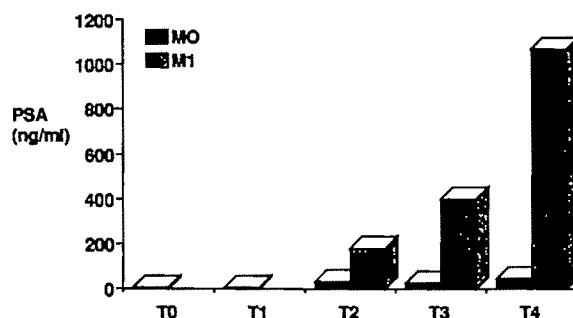


Fig. 1 Mean serum PSA levels in patients with M0 and M1 disease according to T category.

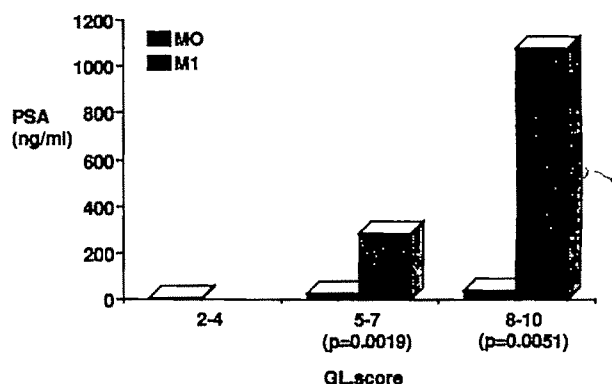


Fig. 2 Mean serum PSA levels in patients with M0 and M1 disease according to Gleason score.

Table 1 Serum PSA Levels with T Categories of M0 Disease

	M0				
	T0	T1	T2	T3	T4
PSA (ng/ml)	0.5-32.4	0.6-12.6	7.7-84	15.8-30	16.4-79
Mean	7.16	8.56	32.51	23.7	47.66

Table 2 Serum PSA Levels with T Categories of M1 Disease

	M1				
	T0	T1	T2	T3	T4
PSA (ng/ml)	—	—	48.8-466	57-2630	46-3428
Mean	—	—	179.36	397.43	1064.86

Table 3 Serum PSA Levels with 3 Ranges of Gleason Score in M0 and M1 Disease

	M0			M1		
	(2-4)	(5-7)	(8-10)	(2-4)	(5-7)	(8-10)
PSA (ng/ml)	0.5-32.4	7.8-65	7.7-79	—	57-1267	46-3428
Mean	5.49	27.11	38.9	—	283	1079.2

Although mean serum PSA levels showed a rising trend with increasing T category and increasing Gleason score, there was a considerable scatter between individual patients.

The relative incidence of M0 and M1 disease for T0-T2 and for T3-T4 categories of tumours is shown in Figure 3A; 71% of T3-T4 and only 20% of T0-T2 tumours had M1 disease. The relative incidence of M0 and M1 disease for 3 groups of Gleason score (2-4, 5-7 and 8-10) is shown in Figure 3B; 81% of patients with a high Gleason

score (8-10) but none with a low Gleason score (2-4) had M1 disease. Patients with an intermediate Gleason score (5-7) had equal proportions of M0 and M1 disease. All patients with PSA >100 ng/ml had M1 disease but only 5 patients with PSA below this level (PSA = 46, 48.8, 57, 59 and 71.6 ng/ml) had M1 disease (Fig. 3C).

The efficiency of T category (T3-T4), Gleason score (8-10) and serum PSA (>100 ng/ml) in identifying M1 disease in patients with newly diagnosed carcinoma of the prostate is shown in Table 4. It is evident that the T category is more sensitive but less specific and the Gleason score is more specific but less sensitive, whereas serum PSA is both sensitive and specific in identifying M1 disease with 100% predictive value.

Discussion

Serum PSA in prostate cancer is now the most useful marker in monitoring the response to

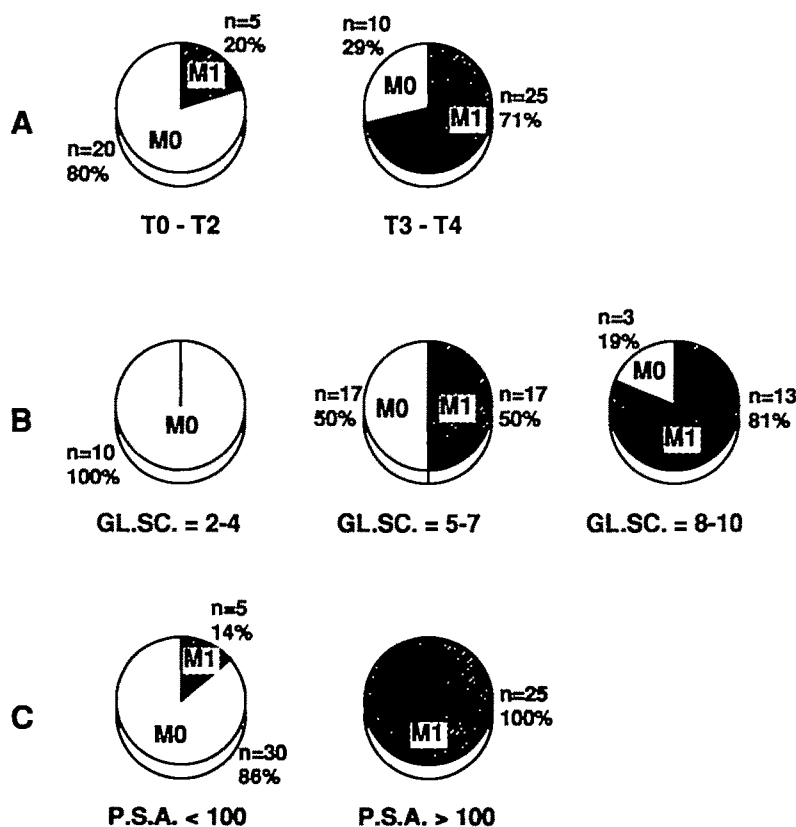


Fig. 3 Relative incidence of M0 and M1 disease with (A) T category, (B) Gleason score and (C) serum PSA level in 60 patients with newly diagnosed CAP

Table 4 Comparative Efficiency of Parameters in Identifying M1 Disease in 60 Newly Diagnosed Patients with CAP

	Sensitivity (%)	Specificity (%)	Predictive value (%)
T3-T4	83.3	66.6	71.4
Gleason score 8-10	43.3	90	81
PSA > 100	83.3	100	100

treatment (Ercole *et al.*, 1987). Tumour relapse or non-response is reflected by a serial rise in PSA levels (Ahmann and Schiffman, 1987; Brawer and Lange, 1989). However, there are limitations with the use of PSA in prostate cancer. If a serum PSA level > 10 ng/ml (Tandem-R assay) is used for the diagnosis of prostate cancer, the positive and negative predictive values are 75 and 77% respectively (Brawer and Lange, 1989). The contribution of surrounding benign hyperplastic tissue and of tumour grade to serum PSA has been reported to be unpredictable (Oesterling *et al.*, 1988; Partin *et al.*, 1990). Thus the original hope that the pre-operative PSA level could provide a "crystal ball" for staging prostate cancer prior to radical prostatectomy is now fading (Lange, 1990).

In this study a significant increase was observed in the serum PSA level in patients with M1 disease. This may be due to the following reasons:

- (1) 71% of patients with T3-T4 tumours and only 20% of those with T0-T2 tumours had M1 disease. Thus local extension of prostate cancer contributed to a rise in serum PSA.
- (2) 81% of patients with a high Gleason score (8-10) and none of those with a low Gleason score (2-4) had M1 disease. Thus high tumour grade also contributed to a rise in serum PSA.
- (3) All patients with serum PSA > 100 ng/ml and only 14% of those with serum PSA < 100 ng/ml had M1 disease. Thus the rise in serum PSA in M1 disease may also be due to the volume of metastatic tumour, either overt or covert.

At the other end of the scale, Shearer (1991) pointed out that prostate cancer with serum PSA < 20 ng/ml had almost no clinical significance and therefore a staging bone scan was not necessary in these patients. This view was shared by Chybowski *et al.* (1991), who studied retrospectively a series of 306 patients with prostate cancer and serum PSA levels of 20 ng/ml or less. Only one such patient had a positive bone scan and thus the negative predictive value was 99.7%. Results from our prospective

study of patients with newly diagnosed prostatic cancer also support their view.

In the present series, although the mean serum PSA showed a rising trend with increasing T category and Gleason score, there was a considerable scatter. Hence we agree that PSA is less useful in predicting pathological stage in individual patients, although it correlates with pathological stage and tumour volume when studied as a group (Oesterling *et al.*, 1988; Partin *et al.*, 1990).

We observed a consistently higher serum PSA level with increasing Gleason score. This was more pronounced in M1 disease than in M0 and the difference was statistically significant ($P=0.0003$). This does not support the view that a high grade tumour produces a low level of antigens (Partin *et al.*, 1990).

This study highlights not only the level of PSA but also stresses the importance of T category and Gleason score in identifying the metastatic potential of prostate cancer at presentation. A serum PSA level > 100 ng/ml (Tandem-R assay) proved to be the most reliable marker in identifying M1 disease, with 100% specificity and 100% predictive value. With this measurement alone, the majority of patients with M1 disease (83%) could be correctly identified (predictive value=100%). For the remaining 17%, however, we advocate a high index of suspicion if the category is T3-T4 on DRE (predictive value=71.4%) and if the Gleason sum score is 8-10 (predictive value=81%).

It is concluded that when the serum PSA level is already above 100 ng/ml, DRE reveals a T3-T4 category tumour and the Gleason sum score is 8-10, then such a tumour is invariably metastatic (M1). This should preclude, therefore, the need for a routine battery of invasive and non-invasive radiological and other investigations to identify metastatic disease in these patients with carcinoma of the prostate.

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Squamous Metaplasia in the Penile Urethra due to Oestrogen Therapy

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Summary—Histological examination was performed on the anterior penile urethra from 21 asymptomatic trans-sexual patients taking oestrogens prior to surgery. Squamous metaplasia was present in 15 of these patients and in 1 man taking progesterones. Immunohistochemical staining for oestrogen receptors in the urethra was negative. Severe squamous metaplasia was associated with patchy chronic inflammatory cell infiltration but this was also present in normal controls. The lack of recognised complications of squamous metaplasia at this site suggests that it is an incidental observation in men taking oestrogens.

Squamous metaplasia induced by exogenous oestrogens is well described in the glandular epithelium of the prostate (Moore and McLellan, 1938). The influence of oestrogens on other sites in the genitourinary tract has been studied less because of a paucity of biopsy material. Trans-sexual men undergoing surgical gender reassignment provided a means of studying this area because they had frequently been taking oestrogen preparations prior to their operation. We examined the anterior penile urethra from 25 cases and discuss the implication of squamous metaplasia in the male urethra.

Patients and Methods

Twenty-one male trans-sexuals undergoing penile resection for gender reassignment were the subject of this study. All had taken oestrogens as part of their attempts to acquire female characteristics. The nature of the study was explained to the patients, who completed a questionnaire concerning their sexual practices and drug history. Three control cases were studied; 2 of these were autopsies and the third was a trans-sexual male not taking oestrogens. The last patient was a man taking a progesterone preparation who gave no history of taking oestrogens.

The gender reassignment operation consists of removal of the external genitalia and construction of a vaginal tube using penile and scrotal skin flaps. The urethra was opened in the proximal part and a sound inserted at this point, thus avoiding trauma to the anterior urethra, which was removed with the corpora.

The excised penis was fixed in formalin and cut into transverse sections. The specimen contained the anterior and meatal urethra, which was dissected out and entirely processed for standard histological examination. Each specimen yielded 15 to 20 transverse urethral sections and each was stained with haematoxylin and eosin. The urethra was examined by light microscopy and the degree of squamous metaplasia assessed by a simple grading system: Grade A, normal urethra; Grade B, focal squamous metaplasia affecting less than 50% of the urethral lining; Grade C, squamous metaplasia affecting more than 50% of the urethral lining but not extending into the periurethral glands; Grade D, squamous metaplasia affecting more than 50% of the lining and involving the periurethral glands.

Selected sections were then stained for glycogen using periodic acid schiff (PAS) stain and for neutral mucin using diastase-washed PAS-stained sections. The presence of oestrogen receptors was assessed using a monoclonal antibody (ER-ICA,

Abbott Laboratories) on 11 paraffin processed specimens and control sections using a previously published method (Shintaku and Said, 1987). A further 2 penises were obtained fresh and frozen sections stained immunohistochemically for oestrogen receptors with the same monoclonal antibody. In 4 cases the chronic inflammatory cell population was characterised immunohistochemically using monoclonal antibodies to leucocyte common antigen (Dako), T cells (Dako T1) and B cells (L26).

Results

The 21 trans-sexual men who had been taking oestrogens were aged between 21 and 52 years, with most of them less than 35 years old. All denied a history of venereal disease and no urinary tract symptoms were reported. However, 1 patient was HIV positive and another had a history of hepatitis. Thirteen of the 21 had been passive partners in homosexual intercourse and 5 had a history of heterosexual intercourse. There was no history of urethral trauma or instrumentation. Although all 21 men were taking oestrogens, drug histories were available in only 10 and even these were incomplete. The oestrogen preparations used, the dosage regime and mode of delivery varied greatly, probably reflecting the diverse geographical origin of the

patients (Table). All of the men had ceased taking oestrogens for at least 2 weeks prior to surgery to prevent post-operative complications. Two had not taken hormones for 1 year before the operation.

The 3 control patients and 6 of the trans-sexuals taking oestrogens had a normal penile urethra lined by pseudostratified columnar epithelium. The peri-urethral glands were lined by goblet cells secreting PAS positive, neutral mucin. The necks of the glands were connected to the urethral lumen (Fig. 1). The remaining 16 patients had squamous metaplasia of the urethra. In 5 cases this was focal (grade B) (Fig. 2) and in 5 it was widespread but did not involve glands (grade C) (Fig. 3). In 6 patients the metaplasia was extensive and extended into glands (grade D) (Fig. 4); this group included the one patient taking progesterone only. The metaplastic squamous epithelium was non-keratinising and composed of vacuolated cells rich in glycogen, resembling normal vaginal mucosa. When periurethral glands were replaced by squamous epithelium there was concomitant loss of mucus-secreting cells.

Patchy chronic inflammatory cell infiltrates were common in the subepithelial connective tissue and within the urethral lining. These were seen in both the control and test groups. More prominent chronic inflammatory cell infiltration was seen around

Table Characteristics of the Trans-sexual Patients from whom Drug Histories were Available

Nationality of patient	Age (years)	Drug	Duration (years)	Dose (mg)	Frequency	Ended	Gd *
German	25	Progynova (oestradiol valerate)	5	100	3-weekly	4/52	C
Dutch	39	Ethinylloestradiol	2	50	Daily	3/52	A
British	36	Ethinylloestradiol	2	1	Daily	2/52	D
British	28	Premarin (conjugated oestrogens)	2	2.5	× 2/day	2/52	C
French	28	Estraderm (oestradiol)	2	?	× 1/week	3/12	A
Turkish	26	Oestrogen injection	2	?	× 1/month	1 year	C
Finnish	37	Dianova (cyproterone ethinylloestradiol)	14 months	?	Daily	2/52	A
British	52	Premarin	2	2.5	× 3/day	3/52	C
Malaysian	26	Premarin	5	2.5	Daily	2/52	A
Italian	27	Progynova depot	5	100	× 1/month	6/12	D
French	35	Proluton (hydroxyprogesterone decanoate)	15	100	Irregular	1 year	D

*Gd = grade of squamous metaplasia (see text)

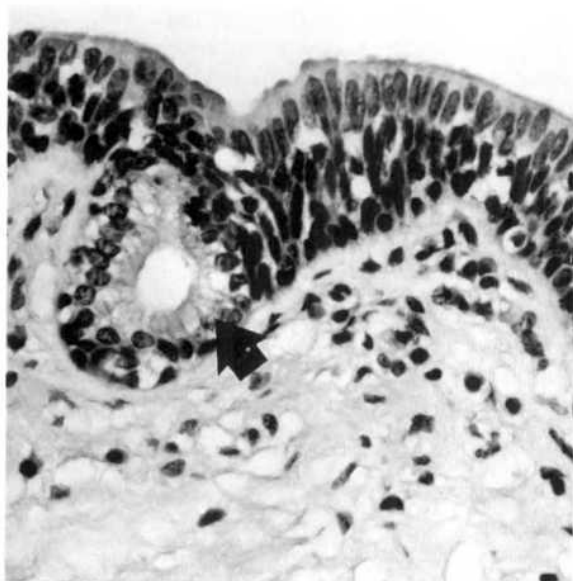


Fig. 1 Normal anterior urethral lining of pseudostratified columnar epithelium with a duct opening from a periurethral gland (arrow). (H and E $\times 380$.)

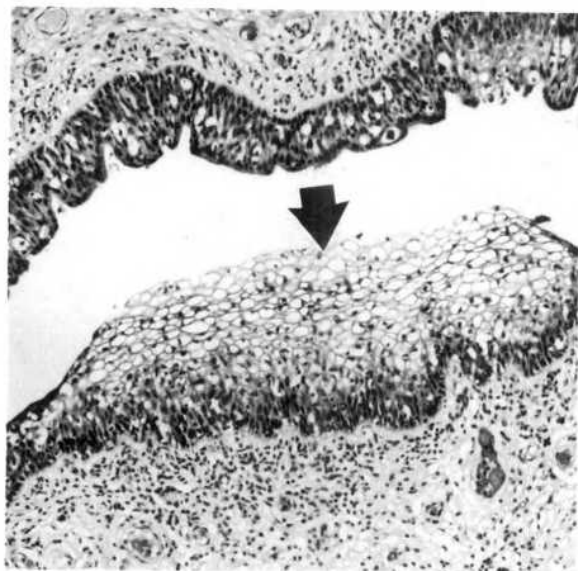


Fig. 2 Focal squamous metaplasia (arrow). Note the associated chronic inflammatory cell infiltrate. (H and E $\times 98$.)

periurethral glands whose lining was replaced by squamous epithelium. Immunohistochemistry showed most of the lymphocytes to be T cells in both test and control patients, although B cells were prominent in patients with extensive squamous metaplasia.

No oestrogen receptors were detected in any of

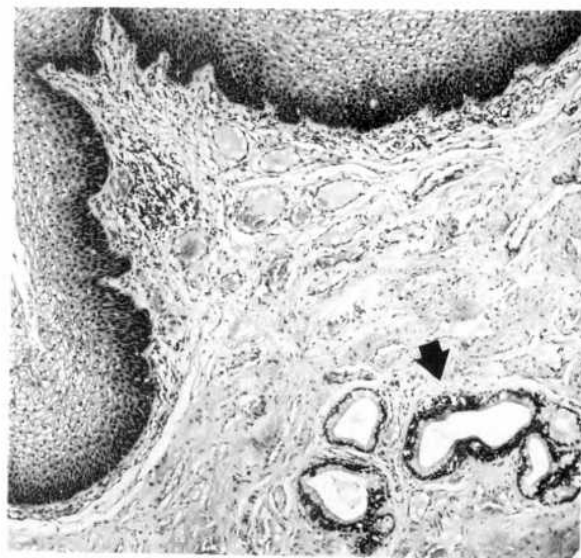


Fig. 3 Extensive squamous metaplasia of the urethra not involving the periurethral glands (arrow). (H and E $\times 98$.)

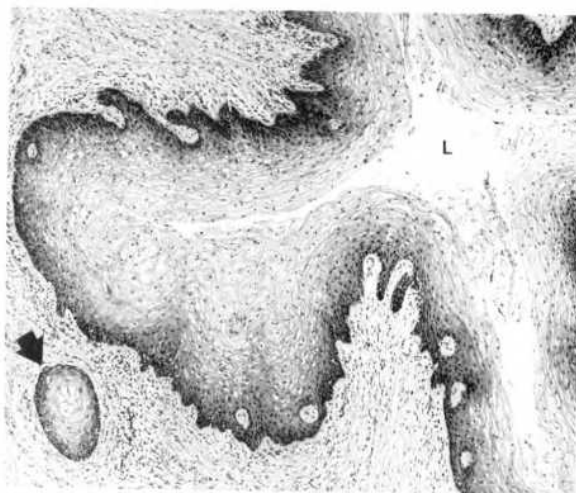


Fig. 4 Total squamous metaplasia (L = urethral lumen) involving the periurethral glands (arrow). (H and E $\times 98$.)

the cases. Initially, formalin fixed tissue was used for the assessment of the oestrogen receptors because of published reports of methods for their detection in this type of material. When our results were negative, we repeated the investigation on fresh urethra, snap frozen and using the manufacturer's method. Once again we failed to demonstrate the presence of the receptors.

Discussion

This study has shown that squamous metaplasia of the male anterior urethra is a common response to

oestrogen therapy. This may be extensive and involve the periurethral glands. In our small study group the drug regimes and doses were too varied and incompletely recorded to permit conclusions to be drawn about duration, dosage and type of oestrogen needed to produce squamous metaplasia. Indeed some patients who had taken hormones for several years showed no changes, whereas others who had taken them for shorter periods had marked metaplasia. The shortest recorded length of exposure to produce squamous metaplasia in our group was 2 years. The effect of oestrogens seems to persist for a considerable time after cessation of administration, as demonstrated by the man who had stopped taking oestrogens 1 year before his operation but who had extensive squamous metaplasia.

It is noteworthy that the one patient who had been taking a pure progesterone preparation had extensive squamous metaplasia of his urethra. This effect has not been reported but progestones have far fewer therapeutic uses in the male and experience is therefore more limited. In view of the problems in obtaining accurate drug histories from the study group we cannot rule out the possibility that this man had also taken oestrogens.

We failed to detect oestrogen receptors in the urethral epithelium regardless of whether normal or metaplastic tissue was examined. This is in keeping with studies in the dog, which showed that oestrogen receptors are confined to the prostatic stroma and the nuclei of transitional epithelium of the prostatic urethra (Schulze and Barrack, 1987). The mechanism of action of oestrogens in inducing squamous metaplasia in the absence of oestrogen receptors must be indirect, but remains obscure.

None of our patients complained of urinary tract symptoms. This is perhaps a little surprising in view of the extent of the changes in the severe cases and the associated chronic inflammation. Squamous metaplasia associated with the acquisition of oestrogen receptors in the female trigone ("pseudomembranous trigonitis") is known to be associated with a syndrome of urinary frequency (Stephenson *et al.*, 1989). Trigonal squamous metaplasia can also occur in the male taking oestrogens (Henry and Fox, 1971). Squamous metaplasia in the verumontanum of the prostatic urethra of a trans-sexual male taking oestrogens resulted in urinary obstruction (Goodwin and Cummings, 1984). Possibly squamous metaplasia in the distal urethra is better tolerated than at proximal sites. Perhaps our patients had not had the changes long enough for them to result in

symptoms. The presence of extensive squamous metaplasia in these patients could lead to confusion when interpreting urine cytology specimens.

Metaplastic epithelium can be the site of malignant transformation. There is no evidence that men taking oestrogens have an increase in penile squamous cell carcinoma and none of our patients showed any evidence of dysplasia. Nevertheless, prolonged oestrogen therapy causes profound alteration to the urethral lining in men. Whilst this might be regarded as an appropriate alteration of the male urethra to a more female histological type, it will be interesting to see if these men develop complications as a result of this hormone-induced metaplasia.

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Value of Testicular Ultrasound in the Evaluation of Blunt Scrotal Trauma without Haematocele

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Summary—The value of ultrasound in testicular trauma with haematocele has been questioned inasmuch as the injured testis should always be explored surgically. Ultrasonography, however, plays an important role in the diagnosis and follow-up of patients with blunt scrotal trauma without haematocele.

We have evaluated 17 such patients with real-time ultrasound. In 9 cases the testis and epididymis were normal to palpation, although in 6 of them parenchymal lesions, mainly subcapsular haematomas and parenchymal contusions not amenable to surgical intervention, were detected with ultrasonography. Seven patients presented with changes in the testicular or epididymal morphology at palpation and in 1 case the testes were not palpable.

Ultrasonography was of great value, indicating surgery in 6 of these patients where physical examination alone was not sufficient to establish the need for surgical exploration.

Since the report by Albert (1980), testicular ultrasound has been used as a complementary examination in the evaluation of scrotal trauma and has shown good specificity and sensitivity (Friedman *et al.*, 1981; Anderson *et al.*, 1983; Jeffrey *et al.*, 1983; Lupentin *et al.*, 1983; Fournier *et al.*, 1985; MacDermott *et al.*, 1988). Its value in the presence of a clinically evident haematocele has been questioned (Cass, 1983; Vaccaro *et al.*, 1986), as surgical exploration has shown better results than conservative management (Cass and Luxenberg, 1988), suggesting that surgery should be undertaken regardless of the results of ultrasonography. Testicular ultrasound is indicated in cases of a traumatised scrotum with normal or swollen testes but without evident haematocele and in cases of scrotal oedema, haemorrhage or previous hydrocele that preclude palpation of the underlying testis.

We present 17 patients with blunt testicular trauma without haematocele who were evaluated with ultrasound.

Patients and Methods

Between 1986 and 1990 we have seen 17 patients with testicular contusion without haematocele following blunt scrotal trauma. Their ages ranged from 4 to 40 years (mean 23.4). There was no known history of scrotal abnormalities before injury. The most common aetiology was sports-related activity (10 patients), followed by injury at work (3), assault (2), traffic accident (1) and domestic lesions (1).

Real-time scrotal ultrasonography was performed in every case, using a 7.5 MHz transducer. Patients treated conservatively were followed up with ultrasound scans.

Results

On physical examination the testes were always palpable, except in 1 patient in whom scrotal inflammation and oedema precluded palpation. In this patient ultrasonography showed normal testes (Table). Nine patients presented with normal testes and epididymes at palpation, although ultrasound detected 2 sub-tunica haematomas (Fig. 1), 2 parenchymal contusions (Fig. 2) and 2 cases of

Table Comparison of Physical Examination, Ultrasonography and Treatment

Patient no.	Physical exploration	Ultrasound	Management
1	Diffuse swelling of the whole scrotum	Thickened scrotal layers, normal testes	Conservative
2	Tender normal testes and epididymes	Minimal bilateral hydrocele	Conservative
3	Tender normal right testis	Normal testis	Conservative
4	Scrotal haematoma with tender normal left testis	Thickened oedematous scrotum, normal testes	Conservative
5	Tender normal right testis	5-mm sub-tunica haematoma	Conservative
6 (Fig. 1)	Tender normal right testis	Double sub-tunica haematoma 15 and 5 mm	Conservative
7	Tender normal left testis	8-mm intratesticular contusion	Conservative
8 (Fig. 2)	Tender normal left testis	Contusion of upper testicular pole	Conservative
9	Scrotal haematoma with tender normal right testis	Thickened scrotum and slight inflammation of tail of epididymis	Conservative
10	Superficial scrotal haematoma with tender normal left testis	Inflammation of tail of epididymis	Conservative
11	Tender normal left testis with enlarged tail of epididymis	Inflammation of tail of epididymis	Conservative
12 (Fig. 3)	Tender normal left testis with enlarged epididymis	25-mm haematoma-contusion of epididymis	Surgical drainage
13	Right tender testis with a small palpable nodule in the lower pole	Sub-tunica haematoma 20 × 10 mm in lower pole and 5-mm intraparenchymal haematoma	Surgical drainage
14	Tender right swollen testis	Contusion of 2/3 of testis	Orchiectomy
15 (Fig. 4)	Tender right swollen testis	Contusion of 90% of testis	Lost, orchiectomy
16 (Fig. 5)	Tender right swollen testis	Intratesticular contusion-haematoma with ruptured tunica	Surgical repair
17	Tender right swollen testis	Intratesticular contusion-haematoma of lower pole with ruptured tunica	Surgical repair

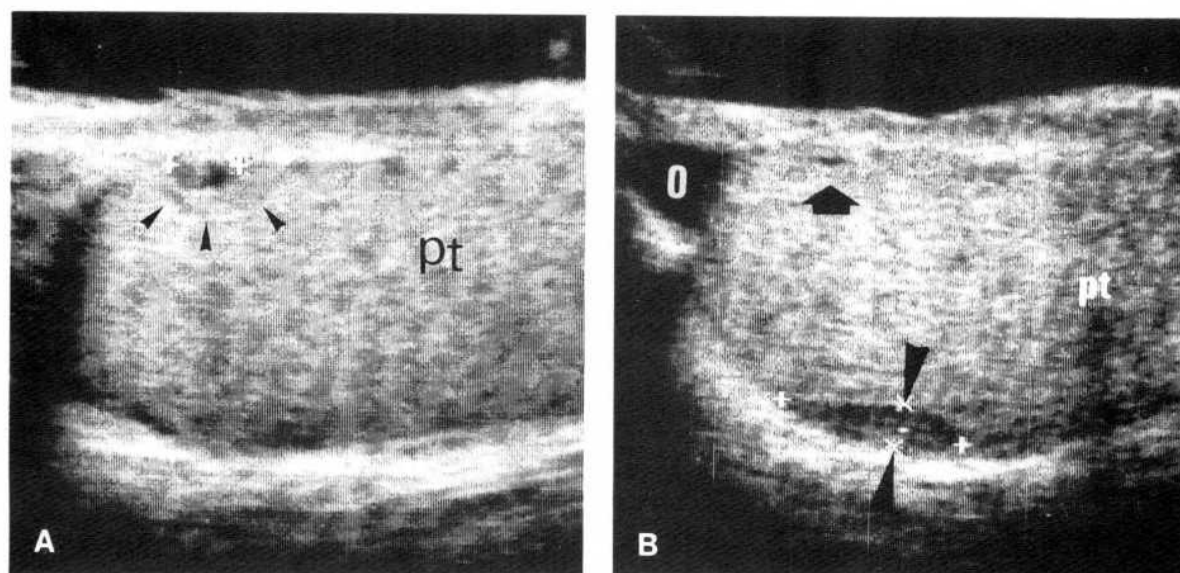


Fig. 1 (A) Longitudinal scan of right testis showing normal testicular parenchyma (PT) and 5-mm focal sub-tunica hypoechoic lesion surrounded by a sonolucent area (outlined by arrowheads) corresponding to a sub-tunica haemorrhage surrounded by a parenchymal contusion. (B) Parallel scan reveals another hypoechoic sub-tunica area 15 × 4 mm in the posterior aspect of the testis (arrowheads). Minimal hydrocele (0).

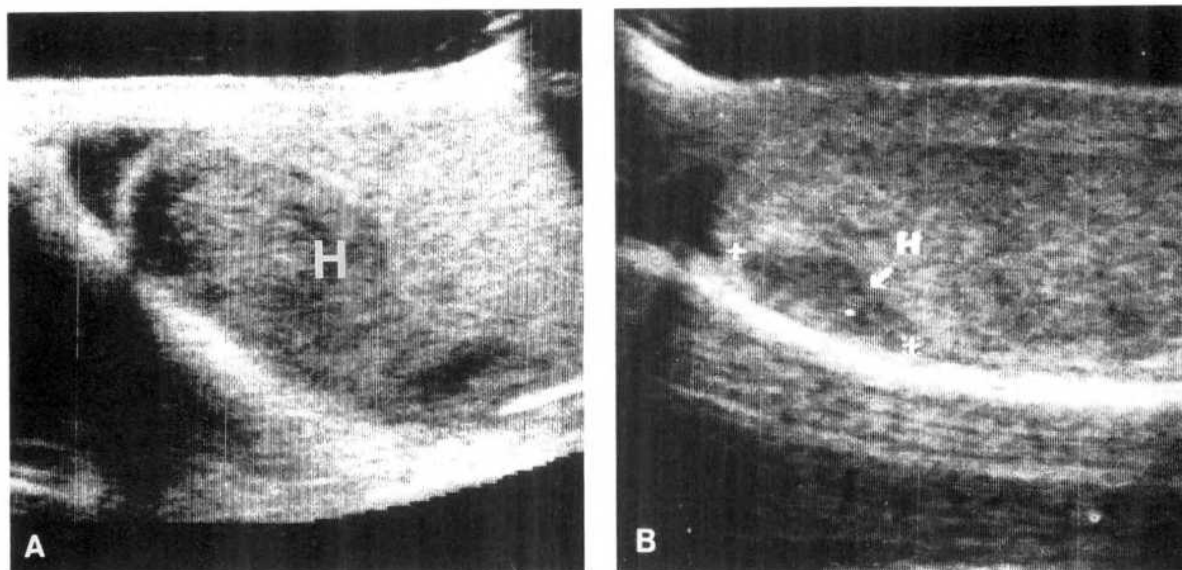


Fig. 2 (A) Longitudinal scan showing hypoechoic area (H) 14×40 mm along the upper pole of the testis corresponding to a parenchymal contusion. (B) Follow-up scan 40 days later shows partial resolution of the lesion.

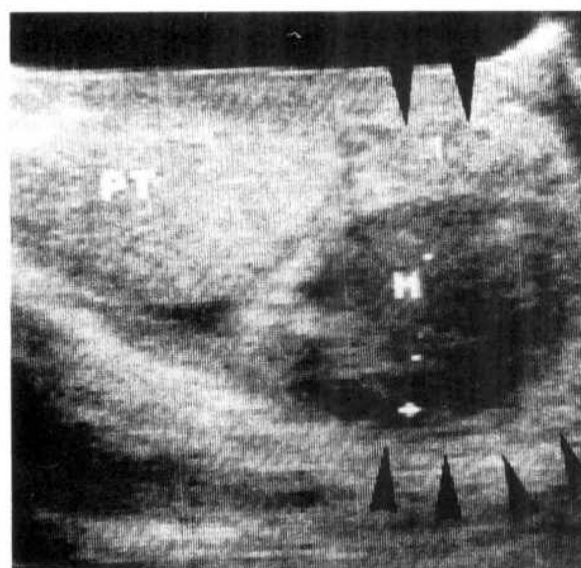


Fig. 3 Transverse scan of normal left testis (PT). Hypoechoic area of 25 mm with internal echoes in the epididymis (M) corresponding to an epididymal contusion and haematoma. Arrowheads outline the limit of the epididymal capsule.

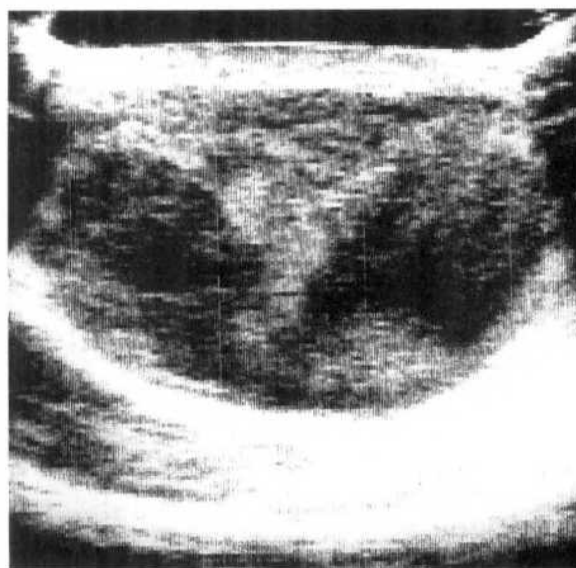


Fig. 4 Longitudinal scan of right testis showing disorganised pattern of echogenicity and 2 focal areas of sonolucency representing a contusion of almost the whole testis with 2 areas of parenchymal infarction and haemorrhage. Neither testicular rupture nor haematocele was detected.

epididymitis; none required surgery and all were managed conservatively.

Seven patients (nos 11–17) presented with palpable testes but with a variety of changes in the testicular or epididymal morphology (Table). Scrotal ultrasonography showed epididymitis (1 case),

epididymal haematoma (1) (Fig. 3), sub-tunica haematoma (1) and major testicular contusions (4) (Fig. 4); 2 of these 4 patients had a rupture of the tunica albuginea (Fig. 5). Five of these 7 patients were treated surgically: 2 underwent evacuation of the haematomas, 2 debridement of necrotic tubules

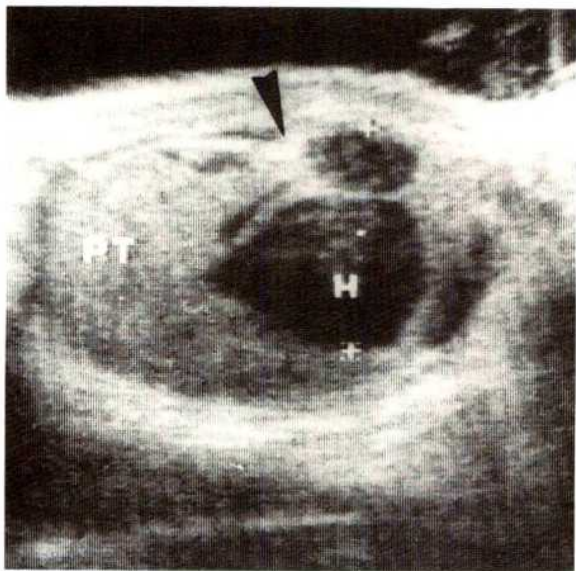


Fig. 5 Oblique scan of right testis showing 2 intratesticular hypoechoic areas (H) corresponding to parenchymal contusions with haematoma. The superior extrudes through the tunica albuginea where a discrete fracture plane (arrowhead) can be seen, representing a testicular rupture without haematocele.

with suture repair of the tunica albuginea and 1 an orchiectomy. All post-operative courses were uneventful. One patient was managed conservatively and 1 refused any kind of treatment.

Discussion

The value of ultrasound in testicular trauma with haematocele has been questioned, since the injured testis should be explored surgically in all cases. Surgically treated patients resume normal activities earlier than those treated conservatively, and the number of orchiectomies is lower (Cass and Luxenberg, 1988). Ultrasonography, however, plays an important role in the diagnosis of blunt scrotal trauma without haematocele (Kratzik *et al.*, 1989).

In the present series, physical exploration diagnosed correctly only 5/17 injuries. Palpation of the testis and epididymis was normal in 9 patients even when ultrasound revealed obvious lesions in 6. However, none of these patients required surgery

and they progressed satisfactorily with conservative management. Ultrasound was helpful in assessing healing of the lesions.

Of 6 patients who presented with a swollen testis or epididymis, 5 underwent surgery (6 if we include no. 15). None had had a haematocele and physical examination alone had not been sufficient to establish the indication for surgical exploration. This was performed only when ultrasound suggested a ruptured tunica, major testicular contusion or testicular or epididymal haematoma. The surgical findings correlated exactly with the ultrasound images.

In view of the good results obtained with conservative treatment of patient no. 8 (Fig. 2), such treatment should perhaps also have been tried in patient no. 13.

We do not know the minimum size of contusion or haematoma for which surgical treatment is indicated. Lesions measuring less than one-third of the testis will probably heal with conservative treatment alone, while the larger lesions or those accompanied by rupture of the tunica will require surgical repair or orchiectomy.

Blunt scrotal trauma without haematocele is difficult to assess by physical examination alone. In the majority of patients in whom the testis and epididymis are normal at palpation no surgery will be needed, although in two-thirds of them a parenchymal lesion exists that is detectable only by ultrasonography. These patients should be followed up with regular scrotal ultrasound examinations until resolution.

When the normal morphology of the testis or epididymis is altered, surgery is needed in a high percentage of cases. Ultrasonography is of considerable value in deciding on surgical or conservative treatment. Contusions or haematomas measuring less than one-third of the testis will probably heal with conservative treatment alone, whereas those that are larger or where the tunica is ruptured will require surgical repair or orchiectomy. Larger series of patients are needed to confirm these recommendations.

In the presence of gross swelling and thickening of the scrotal layers that prevent palpation of the testis, ultrasonography is a rapid method of ascertaining testicular integrity.

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Routine Radio-imaging in Filarial Chyluria—Is it Necessary in Developing Countries?

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Summary—Chyluria is a common presentation of filariasis in developing countries and mostly affects economically poor classes. The judicious use of investigations is mandatory to keep the cost of treatment acceptable. A modified plan is suggested for managing such patients without using retrograde pyelography or lymphangiography.

A total of 54 patients were studied at 2 separate institutions, with retrograde pyelography being carried out at one institution but not at the other. All patients were treated primarily by the instillation of 1% silver nitrate, with an initial success rate of 70%. Eight patients who failed to respond underwent pyelolymphatic disconnection, the success rate being 88%. The omission of retrograde pyelography and lymphangiography had no effect on either treatment or outcome. The value of these radio-imaging techniques is discussed.

Chyluria is a urological manifestation of lymphatic system disease and leads to nutritional deficiency, recurrent clot colic, haematuria and a state of compensated immunosuppression (Arnold and Steele, 1980; Date *et al.*, 1981; Chandra *et al.*, 1988). The conventional diagnostic approach includes confirmation of chyle in the urine, determination of the affected side by cystoscopy, and the demonstration of lymphatico-urinary fistulae by retrograde pyelography and lymphangiography (Diamond and Schapira, 1985). In developing countries, chyluria is found in the poorer classes, and we have attempted to reduce the cost of management by omitting expensive investigations such as retrograde pyelography and lymphangiography.

Patients and Methods

Between 1980 and 1989, 54 patients with chyluria (30 males and 24 females, aged 24 to 43 years) were treated at 2 separate institutions: King George

Medical College (institution A) and Sanjay Gandhi Postgraduate Institute of Medical Sciences (institution B). All patients (32 at institution A and 12 at B) were screened for filariasis; haemoglobin, total and differential counts were made; serum proteins, urea and creatinine were estimated; urine was examined for chyle, acid-fast and other bacilli and intravenous urography (IVU) was carried out. Lymphangiography was performed at institution A in the first few patients but was later omitted for technical and economic reasons. After confirmation of chyluria, patients were subjected to cystoscopy under local anaesthesia. At institution A, a ureteric catheter was introduced on the side of the chylous efflux for 20 to 25 cm and its entry into the renal pelvis was confirmed by the flow of urine. At institution B, its entry into the renal pelvis was confirmed by retrograde pyelography under C-arm fluoroscopy. Thereafter, 5 to 10 ml of 1% silver nitrate were instilled into the pelvicaliceal system in the Trendelenburg position. At institution A, this renal pelvis instillation sclerotherapy (RPIS) was repeated at weekly intervals until chyluria ceased (maximum number of attempts was 4), while at institution B the ureteric catheter was kept

in situ for 2 to 3 days and 1% silver nitrate was instilled thrice daily. Patients who failed to respond to this regimen or who relapsed more than twice were treated by pyelolymphatic disconnection (PLD). The patients were also prescribed long-term diethyl carbamazepine and advised to modify their diet and abstain from hard labour. Follow-up IVU was done 6 to 8 months later to detect any harmful effect on the kidney.

Results

Of 54 patients, 38 (70%) were relieved of chyluria following RPIS. Eight patients developed symptomatic urinary tract infection during or after treatment and were treated with antibiotics. Eight patients who were on the RPIS programme did not comply and were lost to follow-up. A total of 8 patients (5 failures and 3 who had 2 relapses) underwent successful pyelolymphatic disconnection. With one exception, all patients were free of chyluria after 2 years but thereafter only 16 patients were followed up regularly for 2 to 7 years. Five patients relapsed and were again managed by RPIS. Follow-up IVU was performed in only 36 cases, and in 2 of them some changes suggestive of early pyelonephritis were present. One patient at institution B developed a long anterior urethral stricture, probably caused by the combined effects of endoscopy, catheterisation and instillation of silver nitrate. In none of our patients did the degree of pyelolymphatic fistulae demonstrated by retrograde pyelography influence treatment.

Discussion

Chyluria is a common problem in developing countries and usually affects the lower socio-economic classes. It runs a recurrent and chronic course and involves considerable expense and wastage of man hours for both patients and medical personnel. Thus the management of these patients needs to be analysed from a socio-economic angle, particularly because the therapy offered is palliative.

Although a variety of parasitic and non-parasitic factors (Koo and van Langenberg, 1969; Diamond and Schapira, 1985) can cause chyluria, it is generally agreed that it should be considered as filarial unless proved otherwise, particularly in areas where lymphatic filariasis is or was endemic (Ciferri and Glovsky, 1985). Other causes of chyluria, such as tumours, are extremely rare, and hence it is unjustifiable to carry out expensive

radiological investigations in every case. Congenital causes (Arnold and Steele, 1980) do exist but such patients present at an early age, while filarial chyluria usually presents after 2 decades (Okamoto and Ohi, 1983). IVU was carried out in all of our patients and retrograde pyelography in a few, but neither suggested any other cause for chyluria. IVU and the examination of urine for acid-fast bacilli excluded genitourinary tuberculosis, which may occasionally present as chyluria.

The site of the lymphatico-urinary fistulae must be established before commencing treatment (Yu *et al.*, 1978). The most common fistula is the lymphatico-forniceal one (Diamond and Schapira, 1985). Cystopanendoscopy can determine which side is affected by chyluria. Retrograde pyelography and lymphangiography can be used to confirm whether the fistulae are in a calix, the pelvis or the upper ureter, but this information will not alter the usual plan of treatment. Lymphangiography is technically demanding, time-consuming and can cause morbidity (Depalma, 1986); its omission has not caused us any problems. If a lymphaticovenous anastomosis is carried out (Depalma, 1986), lymphangiography is necessary to record accurately the site of obstruction, but the procedure does not have worldwide acceptance because it requires expertise and, even then, results are often unsatisfactory. Retrograde pyelography has been used to delineate the fistulae (Fig. 1). Initially, we thought that the wider the fistulae and the greater their number the

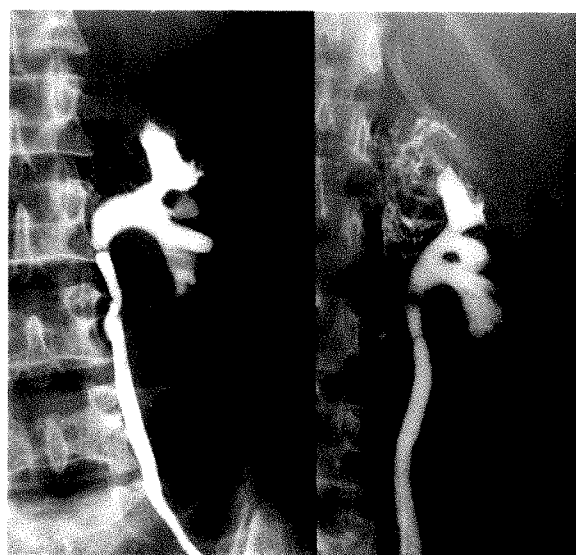


Fig. 1 Retrograde ureteropyelography showing pyelolymphatic fistulae. In (A) only a few are seen but (B) shows multiple fistulae.

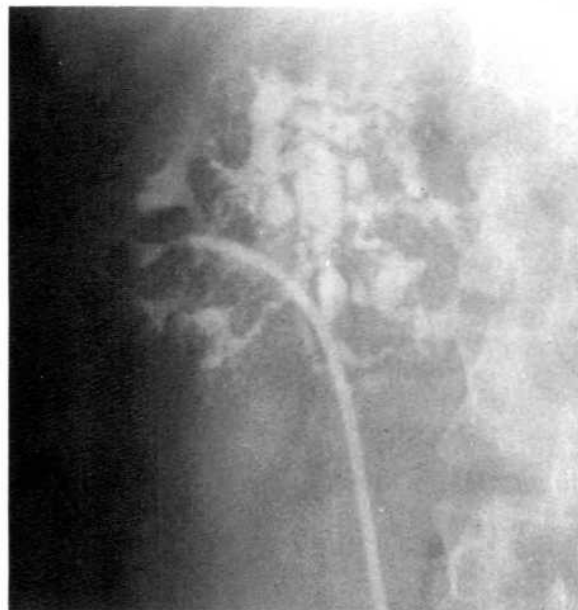


Fig. 2 Retrograde pyelography showing severe degree of pyelolymphatic fistulae.

less likely would be the possibility of control by instillation sclerotherapy; this impression proved to be unfounded (Fig. 2). In the series by Ko-Ko *et al.* (1975), retrograde pyelography failed to demonstrate fistulae in 50% of cases. Pyelolymphatic backflow is not specific to chyluria (Akisada and Tani, 1966) and it is difficult to distinguish it from pyelovenous backflow. Retrograde pyelography is not necessary to check the position of a ureteric catheter because once the catheter has been inserted beyond 20 to 25 cm, a free drip of urine confirms its location in the pelvis.

A preliminary IVU is essential to exclude genitourinary tuberculosis and to obtain baseline information on renal function and the anatomy of the pelvicaliceal system.

Our experience leads us to recommend that patients with chyluria in tropical countries can be managed without retrograde pyelography and

lymphangiography. Intravenous urography, however, should be carried out before and after treatment.

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PAEDIATRIC UROLOGY

Comparison of DMSA Scintigraphy with Intravenous Urography for the Detection of Renal Scarring and its Correlation with Vesicoureteric Reflux

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Summary—A series of 208 patients was prospectively assessed for reflux nephropathy by intravenous urography (IVU) and ^{99m}Tc -dimercaptosuccinate (DMSA) scintigraphy. All patients were studied at least 3 months after their most recent urinary tract infection and micturating cystourethrography (MCU) was performed prior to the scintigraphic studies. DMSA scintigraphy detected significantly more cortical abnormalities than did IVU. There was also a correlation between cortical abnormalities in the DMSA studies and the degree of reflux on MCU.

The validity of DMSA as a cortical imaging agent is evaluated and the histological evidence for its efficacy derived from the animal model is reviewed, lending weight to its establishment as the "gold standard" for renal cortical scarring.

Reflux nephropathy remains one of the most important causes of end-stage renal failure in our society. The correlation of renal scarring with the presence of vesicoureteric reflux (VUR) is well established, although a causative role independent of infection has not been fully established and remains controversial.

Intravenous urography has, until recently, been the standard method of renal cortical imaging. Ultrasound and scintigraphy have increasingly assumed a critical role in this area. Initial scintigraphic techniques using ^{99m}Tc -glucoheptonate (Winchell *et al.*, 1971; Handmaker, 1982; Sty, 1987) and ^{99m}Tc -dimercaptosuccinic acid (DMSA) (Enlander *et al.*, 1974; Lin *et al.*, 1974; Bingham and Maisey, 1978) have produced significantly higher rates of detection of cortical abnormalities than IVU.

We report a prospective study in 208 paediatric patients, comparing the detection of renal cortical scarring by intravenous urography and ^{99m}Tc -

DMSA scintigraphy. The scintigraphic techniques were critically evaluated. A correlation between renal cortical scarring and grade of VUR determined by micturating cystourethrography was also found in this prospective analysis.

Patients and Methods

All patients were referred by a paediatric nephrologist and urologist and were prospectively entered into the study over an 18-month period. Those with bacteriological evidence of recent urinary tract infection were specifically excluded from this study and entered into a separate study. Patients in the present study had experienced their last documented urinary tract infection at least 3 months previously.

Patients underwent IVU, MCU and bacteriological analysis of bladder urine prior to the scintigraphic study, which was usually undertaken within 7 days of the MCU.

Sedation. Children who were unable to co-operate or who were less than 18 months of age were sedated

for the scintigraphic studies. A standard protocol of oral pentobarbitone 5 mg/kg (maximum 100 mg) was administered 1 h prior to the study as well as either intramuscular pethidine 1.5–2.0 mg/kg (maximum 75 mg) and/or droperidol 0.05–0.20 mg/kg (maximum 3.5 mg) 30 min prior to the study. The children were under close supervision by medical and nursing staff before, during and after the study and were usually admitted on a day-only basis for this purpose.

Intravenous urography. All studies were performed with non-ionic contrast medium (Omnipaque 240) at a dose of 1.5–2.0 ml/kg with a minimum dose of 10 ml and a maximum dose of 40 ml for children up to 12 years of age. Above this age, 1 ml/kg was administered. Each study comprised 4 plain films with no additional tomography of the kidneys.

Dose. The dose of ^{99m}Tc -DMSA was based on the adult dose of 100 MBq and corrected for age using the following formula:

$$\text{Dose} = \frac{(\text{age} + 1) \times \text{adult dose}}{(\text{age} + 7)}$$

The minimum dose was 40 MBq.

Imaging. Imaging was performed 3 h after injection in the supine position. All studies were performed on a General Electric 400AT gamma camera interfaced to a dedicated computer. Normal planar images were acquired in the anterior and posterior projections for 5 min per image using a high resolution collimator. Each kidney was separately imaged for 100K counts using a pinhole collimator with a 5 mm aperture.

SPECT (single photon emission computed tomography) was undertaken in 76% of patients. Counts were acquired in an elliptical orbit using 64 projections with 30 s per stop. Following the application of a Hanning pre-filter, images were reconstructed using back projection and a ramp filter. The counts from the anterior and posterior images were used to calculate differential renal function by the geometric means of anterior and posterior counts for each kidney. The posterior planar image was used for reporting purposes.

Reporting criteria. VUR was graded according to the international classification (Levitt *et al.*, 1981) (Table 1). Renal scarring was reported as occurring in the upper, middle and/or lower poles of each kidney in both IVU and DMSA studies in order to enable comparison of the sites of scarring.

Table 1 International Classification of Vesicoureteric Reflux

1. Ureteric reflux only.
2. Reflux to pelvicaliceal system, with no dilatation and normal fornices.
3. Mild—moderate dilatation of the ureter and pelvicaliceal system with normal or slightly blunted fornices.
4. Moderate dilatation of ureter and pelvicaliceal system with obliteration of fornical angles but maintenance of the papillary impressions.
5. Gross dilatation of ureters and pelvicaliceal system with loss of the papillary impressions.

The major criteria considered in reporting were:

1. Disruption of the cortical rim of uptake seen in the pinhole images.
2. Clearly defined defects in uptake on the emission computed scans.
3. Significant variation in the left:right relative function was also considered.

The scintigraphic studies were independently reported by 3 experienced nuclear medicine physicians with no knowledge of the radiological findings. Concordant reporting by at least 2 of 3 observers was required for the final report.

The radiological investigations were independently reported by a senior urologist, nephrologist and a staff radiologist in all cases. Concordant reporting by at least 2 of 3 observers was required for the final report.

If no consensus was reached by 2 of 3 observers for all imaging studies, the case was rejected.

Statistical analysis. In statistical analysis of the data, McNemar's test (Armitage and Berry, 1987) was applied to the comparison of IVU and DMSA results as well as the comparison of pinhole and planar images as these were paired and drawn from the same population. The *P* values are expressed using a one-sided approach, and the 95% confidence limits also stated. The relationship between grade of VUR and cortical scarring was analysed by linear regression methods for each major age group.

Results

In all, 208 patients were prospectively studied. One patient had a solitary kidney, giving a total of 415 kidneys studied. The patients ranged in age from 3 months to 12 years (average 3.7 years). The male to female ratio was 1:2.

Intravenous urography demonstrated focal scar-

Table 2 Comparison of DMSA and IVU for Detection of Renal Cortical Scarring by Major Age Groups

Age (years)	No. of patients	IVU - ve DMSA - ve	IVU + ve DMSA + ve	IVU - ve DMSA + ve	Concordance (%)
<1	54	36	7	11	43/54 (80)
1-3	62	39	14	9	53/62 (85)
3-6	47	34	7	6	41/47 (87)
>6	45	22	17	6	39/45 (87)
Total	208	131	45	32	176/208 (85)

ring in 50 kidneys (12%), (21% of patients) and ^{99m}Tc -DMSA in 96 kidneys (23%) (37% of patients) (Table 2). All patients showing scarring on IVU had scarring in the corresponding ^{99m}Tc -DMSA studies. Neither modality showed a positive result in 319 kidneys (77%), (63% of patients), (Table 2). DMSA was significantly better than IVU for detection of renal cortical scarring ($P < 0.001$, 95% confidence limits between 0.097 and 0.20). Of those patients demonstrating scarring in DMSA studies, the male to female ratio was 1:2.

Six patients were found to have unilaterally shrunken kidneys with no focal abnormalities in either the shrunken or contralateral kidney.

SPECT studies were undertaken in 76% of patients. Although the cortical abnormalities were more clearly defined, no new abnormalities were detected compared with the pinhole images, nor were any abnormalities missed. Of the 96 scarred kidneys detected in the pinhole or SPECT studies, 61 were clearly evident in the posterior planar images, 16 were equivocal and 19 appeared normal. Pinhole imaging was significantly better for the detection of cortical abnormalities than planar imaging in the posterior projection ($P < 0.001$, 95% confidence intervals 0.67 to 0.73).

Of the 96 scarred kidneys on DMSA scintigraphy, 64 were unilaterally scarred. Differential function analysis in the subset of patients with unilateral scarring demonstrated that 33 (52%) had $>10\%$ difference in function between the normal and scarred kidney (10% is the level of significance for differential function, as the error in estimation of the counts for each kidney by this methodology is 5%).

Concordance for site of scarring and renal outline was present in 79% of kidneys on both DMSA and IVU in patients in whom scarring was detected by both modalities. Although no kidney with cortical scarring on IVU was missed in the DMSA study, there was a small degree of variation in the sites detected. Thus 24% of kidneys had extra sites of

involvement on DMSA only, while 15% had extra sites on IVU alone.

A total of 269 kidneys had evidence of grades 1-3 VUR on MCU, while 34 had grades 4-5 VUR; 112 kidneys had no MCU evidence of VUR (Table 3). There was a marked decrease in the incidence of VUR with increasing age, especially after the age of 6 years. Using regression analysis with a linear fit to the data, a correlation coefficient of 0.89-0.91 was found between grade of VUR and cortical scarring for the major age groups.

DMSA evidence of scarring according to age is shown in Table 3.

Discussion

The current study demonstrates several important features. There is a higher rate of detection of renal cortical abnormalities by scintigraphy than by intravenous urography, with DMSA detecting scarring in significantly more kidneys than IVU. This confirms the work of several other authors

Table 3 Incidence of DMSA Abnormalities by Age and Degree of Vesicoureteric Reflux

Age (years)	Grade VUR	No. of kidneys	DMSA abnormalities (%)
<1	0	21	0
	1-3	73	8 (11)
	4-5	15	8 (55)
1-3	0	19	1 (5)
	1-3	71	11 (15)
	4-5	6	4 (67)
3-6	0	31	7 (23)
	1-3	79	24 (30)
	4-5	8	7 (88)
>6	0	45	7 (16)
	1-3	46	7 (15)
	4-5	5	4 (80)

(Bingham and Maisey, 1977; Merrick *et al.*, 1980; Goldraich *et al.*, 1989). However, it raises the question of the "gold standard" for imaging of cortical scarring. The evidence that DMSA is this "gold standard" has, up to now, been inferred from a number of observations in human and animal studies. The current body of knowledge is based on several observations:

1. The matching of cortical defects on DMSA studies with the sites of IVU scarring (Smellie *et al.*, 1988).
2. The reproducibility of the sites of absent uptake of DMSA in sequential studies (Goldraich *et al.*, 1989).
3. Histologically confirmed pyelonephritis leading to loss of cortical function and causing defects in uptake in the piglet model of VUR (Rushton *et al.*, 1988).

The conclusive evidence that sites of renal cortical abnormalities on DMSA scanning are indeed areas of focal scarring comes from the work of Arnold *et al.* (1990), based on the piglet model. They established histologically-confirmed scarring in 60 piglets and found DMSA scintigraphy to have a high level of correlation with sites of macroscopic scarring. The sensitivity and specificity of DMSA for the detection of cortical scarring were 85 and 97% respectively, with 4 instances of scarring being missed. Of the 4 sites missed, 3 were minor degrees of scarring and only 1 major scar went undetected. The study acknowledged the comparatively poor quality of the imaging due to large pixel size and acquisition in the anterior and posterior projections with no oblique or pinhole images. A very high specificity was noted in this study.

Perhaps the most important quantum of evidence for the validity of DMSA as a cortical imaging agent in the human is in that group of patients in the current study where scarring was detected by both modalities, where there was a 79% concordance for the sites of scarring. When Smellie *et al.* (1988) reported a study of DMSA imaging in 54 patients with established radiological scarring they found DMSA and IVU concordance for extent, site and severity of scarring in 63% of kidneys. A similar finding was reported by Goldraich *et al.* (1989), who found concordance for site of scarring in 26 of 30 kidneys (87%).

Further validation that the cortical defects demonstrated by DMSA scintigraphy in the human represent scarring is provided by the constancy of the siting of these defects in sequential scans. Reproducibility was well demonstrated by Goldraich *et al.* (1989) in the annual follow-up of 194

patients for 5 years with DMSA scintigraphy. The siting of defects remained constant in 193 patients over the 5 years of follow-up. Our experience has been similar, albeit in a much smaller group of patients.

Ultrasound imaging of the kidneys is an attractive alternative to cortical imaging as no radiation exposure is involved. Early studies of this modality may have been disadvantaged by the standard of equipment used. A more recent study comparing DMSA, IVU and ultrasound was presented in 1987 by Monsour *et al.* A subset of 63 children in a group of 150 was prospectively studied by all 3 modalities. DMSA detected cortical scarring in 60 children, while ultrasound and IVU detected it in 50 and 36 children respectively. However, when the data were examined by age, a marked disparity in the rate of detection of scarring was found. DMSA was found to be superior to ultrasound in children up to 5 years of age. This disparity between the 3 modalities was progressively lost in the older children. The conclusion was that DMSA scintigraphy was the investigation of choice for the detection of renal scarring in children up to 5 years of age. Unfortunately, ultrasound is a highly operator-dependent procedure, requiring dedicated operators to extract the maximum from each study, and this is not freely available at most centres in Australia.

One of the more important problems associated with the IVU detection of scarring stems from the overlying bowel contents obscuring the renal cortical outline. Much diligent bowel preparation is required on the part of the patient, and even then the images are often unsatisfactory. Tomography has been advocated as a solution but has limited appeal because of the higher radiation dose to the patient. Reliance must therefore be placed on indirect markers of cortical scarring such as distortion of the calices and the distance of the upper pole calices from the lumbar vertebrae. The paucity of perirenal fat in many young children also leads to a loss of contrast that is important for the visualisation of the renal cortex in the plain film.

In our experience, the pinhole image offers better resolution of cortical uptake and greater sensitivity for the detection of abnormalities than the posterior planar image. The problem of attenuation of the polar regions due to the pinhole effect is not a limiting one, because of the size of the kidneys in this paediatric group and also because of the collection of an appropriate number of counts. In particular, a stripe of more intense uptake is seen delineating the cortical outline, interruption of which is indicative of scarring. SPECT further

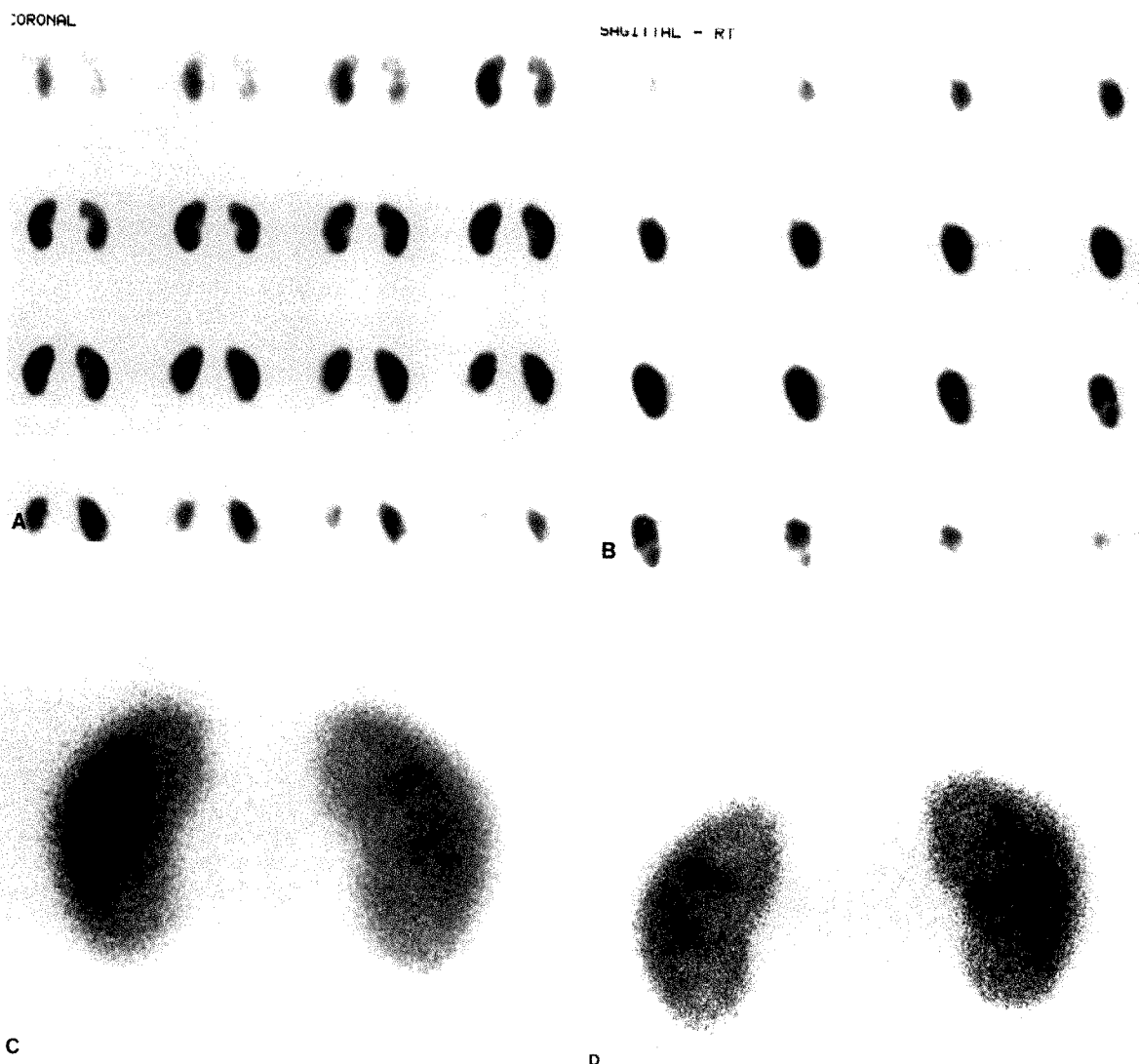


Fig. 1 Normal DMSA study. A and B demonstrate tomographic images obtained in the coronal and sagittal projections respectively. The cortical stripe of increased uptake is clearly seen in all projections. C is the planar image in the posterior projection from the same patient. It shows good visualisation of the reniform outline, but the cortical delineation is not as clearly demonstrated as in the pinhole image in D.

confirms this disruption and gives a better impression of site and extent of the abnormality, although it does not add to the sensitivity of the test. We did not perform oblique planar views in this series because planar views in general do not clearly delineate the stripe of cortical activity seen in both the pinhole and SPECT studies. It is the disruption of this stripe that is germane to the detection of scarring. These extra views would have added to the time of sedation, and as SPECT studies were acquired in a large number of patients, little justification could be made for prolonging each

study. The decision was clearly vindicated by the results, in that no extra lesions were detected in the SPECT studies compared with the pinhole images. By the same token, no lesion detected in the pinhole images was missed in the SPECT studies.

The splenic impression upon the superior and lateral aspects of the left kidney is offered as a reason for the reporting of a higher incidence of scarring on the left side. This is a remote possibility if the techniques outlined above are operational. Scarring of the renal cortex has been described as wedge-shaped or ovoid (Sty *et al.*, 1986; Traisman

et al., 1986), unlike the splenic impression which is a smooth indentation of the cortical outline with no disruption of the stripe of cortical uptake in the pinhole image (Fig. 2). Our result of a higher incidence of scarring on the left side confirms a similar finding by Monsour *et al.* (1987).

The timing of the DMSA study is crucial in any consideration of renal scarring. We studied patients at least 3 months after their most recent urinary tract infection. The importance of this is borne out in the study of 209 patients by Goldraich *et al.* (1989). A small subgroup of 6 patients who had DMSA scans performed at the beginning of an acute urinary tract infection on the background of previous infections showed new areas of decreased cortical uptake. Repeat studies 4 weeks after the urine became sterile revealed resolution of the new areas of reduced uptake in 5 of the 6 children. A reversal of the depression of differential function was also noted. In general, these defects are indistinguishable from scarring except when the scarring is extensive and long-standing and accompanied by changes in the intervening functioning areas of tissue that distort the reniform outline.

Traisman *et al.* (1986) confirmed the transient focal defects in uptake in pyelonephritis. Handmaker (1982) had earlier described the "flare" of reduced uptake associated with renal infection. This referred to the pattern of reduced DMSA uptake radiating from the pelvicaliceal system to the periphery of the cortex that was often multifocal. A similar description had been reported by Hoffman *et al.* (1980) in a study of pyelonephritis in diabetics by computed axial tomography. A similar "flare" of decreased attenuation was seen after administration of contrast in the infected kidneys.

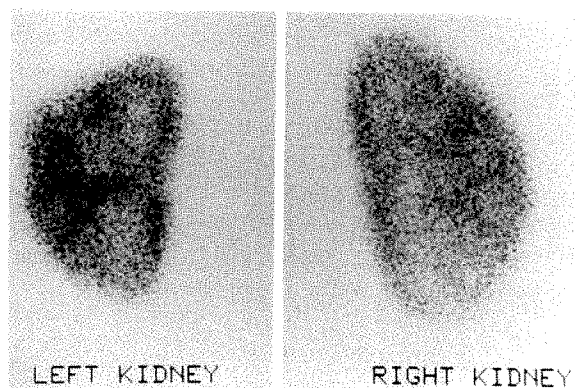


Fig. 2 Normal posterior pinhole DMSA study demonstrating the splenic impression on the superolateral aspect of the left kidney as a smooth indentation, with no disruption of the cortical stripe of activity.

The true incidence of VUR is unknown since most patients diagnosed present with urinary tract infection, whereas others with VUR alone go undetected. Mininberg's review (1986) of 59,645 children aged 4 to 18 years revealed a 2% incidence of bacteriuria and a 14% incidence of VUR. A further study (Abbott, 1984) found VUR in 10% of healthy neonates with negative urine cultures. There is much literature to support the claim that up to 50% of children with urinary tract infection have VUR and, of these, one-third will have reflux nephropathy (Newhouse *et al.*, 1982; Mininberg *et al.*, 1986).

Longitudinal studies demonstrate spontaneous resolution of VUR in 30% of patients over 2 years and overall resolution in up to 80% (Edwards *et al.*, 1977; Normand and Smellie, 1979). Winberg *et al.* (1982) found that children with their first urinary tract infection who were under 1 year of age had a 40% incidence of VUR compared with 25% for those over 1 year of age. Our data have confirmed this trend, with 89 of 109 kidneys (81%) in children under 1 year of age demonstrating VUR compared with 196 of 306 kidneys (64%) in patients over the age of 1 year. We have also shown a progressive decrease in VUR with increasing age for all age groups.

Those children with more severe grades of reflux (4–5) showed a much higher incidence of scarring with increasing age in spite of the overall trend of a decreasing incidence of severe VUR with increasing age. The correlation between grade of VUR and scarring was good for all age groups. Analysis of the data in Table 3 shows 2 distinct trends. First, there was a higher incidence of scarring (53–80%) with more severe grades of reflux in all age groups. Secondly, there was a progressive increase in scarring with increasing age in kidneys with no evidence of VUR. Associated with the decreasing incidence of grades 1–3 VUR, this suggests that there is spontaneous complete regression of VUR, although the more severe grades are less likely to regress (Edwards *et al.*, 1982). Scarring may already be well established in these patients—hence the incidence of scarring in older children with no evidence of VUR.

The other important finding in this group of patients was the presence of 6 shrunken kidneys with no evidence of focal scarring. This problem has recently been addressed by Najmaldin *et al.* (1990), who studied 24 children with antenatally suspected VUR. Of 36 kidneys, 26 had either grade 3 or 4 VUR. IVU was normal in 13 patients, but showed shrunken kidneys with no focal scarring in

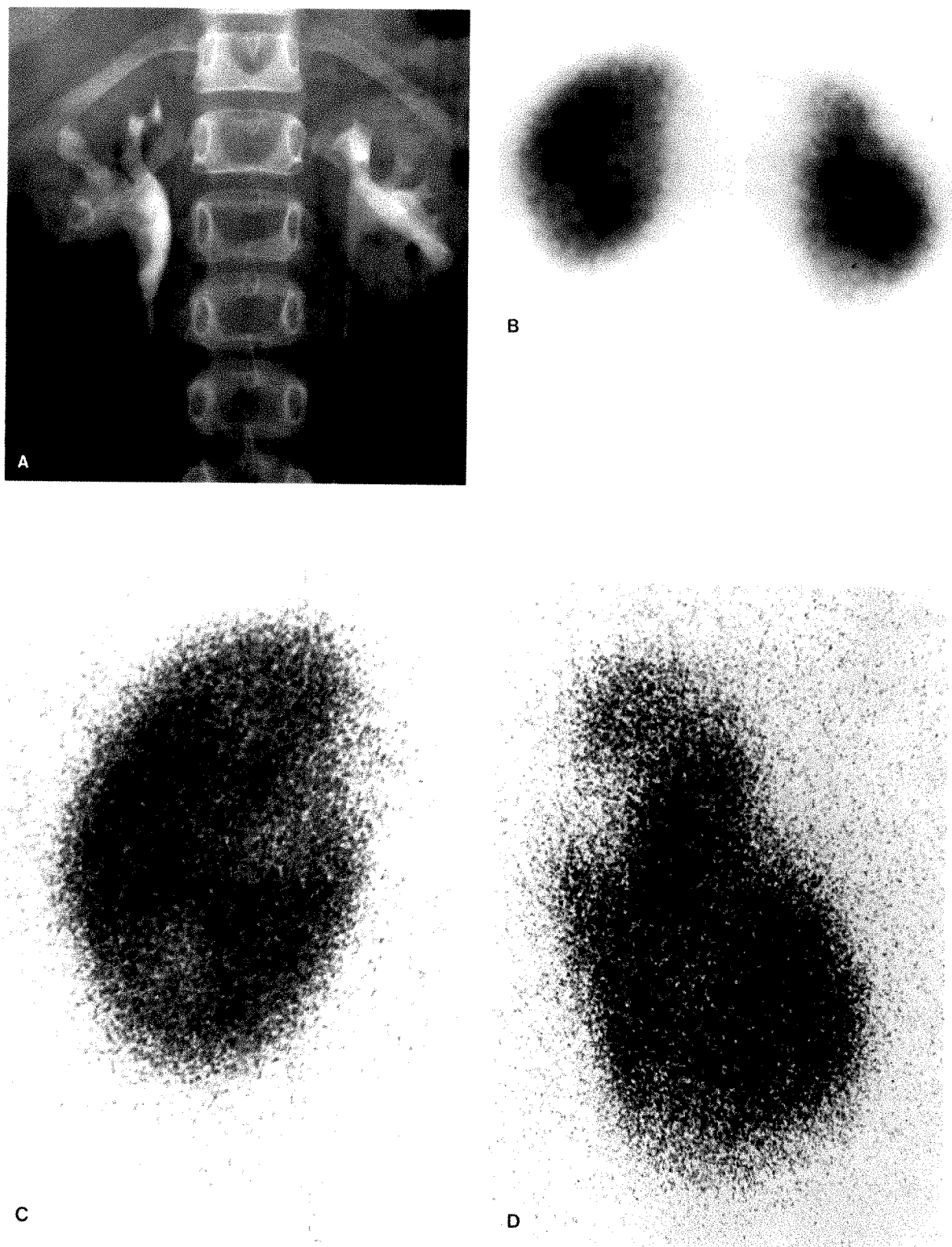


Fig. 3 Abnormal DMSA study demonstrating bilateral renal scarring. (A) IVU study in which bilateral scarring is apparent. (B) Posterior planar DMSA images, confirming several sites of reduced uptake affecting both kidneys. The left kidney is more severely scarred, especially in the upper pole. These abnormalities are more clearly seen in the pinhole views (C and D).

10 kidneys of 7 patients. All 10 kidneys had severe VUR (grade 3 or 4). As all patients received prophylactic antibiotics immediately after birth and the relevant investigation commenced in the neonatal period, the role of infection in the evolution of these changes is unlikely. Severe intra-uterine VUR is the likeliest explanation for the shrunken kidney and as Beck (1971) has shown in the animal model, it may be due to the obstructive effect of severe VUR on the affected kidney in the first half of gestation.

The use of sedation in the paediatric patient is a controversial topic that has no clear-cut answers. It is the accepted practice in this group of hospitals to sedate all young or unco-operative children undergoing imaging procedures. This is usually light sedation, administered in a fully supervised situation on a one-to-one basis. The basic philosophy is that if a child is to be exposed to radiation, the maximum amount of information should be gleaned from the procedure and the benefits of that information should outweigh the small risk attached to sedation.

Imaging and dosimetric considerations

^{99m}Tc -DMSA is usually bound to metalloproteins in the proximal tubule of the kidney, with about 40% of the injected dose localising renally by 3 h (Arnold *et al.*, 1975). It offers a clear cortical outline with no interference from activity in the pelvicaliceal system. This is the advantage of the agent over ^{99m}Tc -glucoheptonate, of which only 10% of the injected dose is renally bound, while a significant proportion is excreted into the collecting system and may interfere with the clarity of the cortical image.

Analysis of the relevant dosimetry for ^{99m}Tc -DMSA and ^{99m}Tc -glucoheptonate according to the most recent data from the International Commission on Radiological Protection (ICRP, 1988) reveals an estimated dose equivalent (EDE) of 0.034 mSv/MBq and 0.024 mSv/MBq (child aged 5 years) respectively. For a minimum and maximum administered dose of 40 MBq and 100 MBq of ^{99m}Tc -DMSA, the EDE is 1.4 mSv and 3.4 mSv respectively. For administered doses of 92 MBq and 555 MBq of ^{99m}Tc -glucoheptonate the EDE is 2.2 mSv and 13.3 mSv respectively. Unfortunately, this stems from the requirement of a higher dose of ^{99m}Tc -glucoheptonate in imaging the renal cortex adequately. Consequently the whole-body dose equivalent is also higher.

The comparative dosimetry for IVU has been shown to be 7.1 mSv for an adult undergoing an

average of 10 films (Padovani *et al.*, 1987). This would clearly have been significantly less for children being exposed for 4 films. It nevertheless highlights one of the major advantages of the use of ^{99m}Tc -DMSA.

This prospective study of 208 patients adds to the body of literature that supports DMSA scintigraphy as the "gold standard" for detecting renal cortical scarring. The evidence for this is more concrete in that there are histological data that areas of diminished uptake are in fact scars, dismissing the assumption that a proportion of these abnormalities were false positive. Undeniably, the IVU conveys important morphological information about the collecting systems, ureters, bladder, urethra and bony structures that DMSA scintigraphy cannot do. The DMSA study is a complementary investigation, providing an estimation of differential renal function as well as conveying, in a reproducible manner, information about the renal cortex. The evidence for its validity is strong, being supported by both a sound animal model and a profusion of clinical studies, as with the model for acute pyelonephritis.

A cautionary note should be made about the timing of the study in relation to acute pyelonephritis in order to avoid the pitfall of transient loss of function being diagnosed as scarring.

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Extracorporeal Shock Wave Lithotripsy for Renal Calculi in Children

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Summary—Fifteen children (8 male and 7 female) with an age range of 18 months to 15 years were treated with extracorporeal shock wave lithotripsy (ESWL) using the Siemens Lithostar. Two children had a history of metabolic stone disease and 1 child had previously undergone open stone surgery. Four children were treated with a ureteric stent in place and 1 nephrostomy was inserted before treatment. All children were treated under general anaesthesia and all of the stones treated were confined to the kidney and ranged in size from 5 mm to a complete staghorn.

The number of treatments ranged from 1 to 6 and generator voltage ranged from 16 to 19 kV with a maximum number of 30,000 shocks to a complete staghorn. Complications were minimal, with 3 children presenting with colic, 1 child requiring a stent and none requiring a nephrostomy after treatment. The overall stone clearance rate at 3 months was 65%.

ESWL provides an effective treatment for selected calculi in children. In the short term, complications are minimal but the long-term effects on children need to be monitored.

Renal calculi are relatively rare in children, estimated as 100 new cases per year in the United Kingdom (Boddy *et al.*, 1987). The advent of extracorporeal shock wave lithotripsy as a non-invasive technique has revolutionised the management of urinary tract calculi. It was considered as a safe and effective treatment for urinary tract stones in adults. The incidence of urinary tract calculi in children, although small, presents a definite clinical problem.

Before ESWL was introduced, it was considered that surgical intervention for the removal of urinary tract calculi was the treatment of choice in children (Williams and Johnston, 1982). Much evidence has accumulated since then on the efficacy of ESWL in treating calculi in children (Newman *et al.*, 1986; Kroovand *et al.*, 1987; Frick *et al.*, 1988). However, concern has also been expressed regarding the theoretical increased risk in treating children with ESWL. Theoretically, relatively more of the kidney

and surrounding tissue is exposed to the high focal zone, and the shock wave may be more detrimental to the growing structures than to mature organs. The Dornier HM3, which has a wide focal zone, presented logistical problems because of paediatric patients' size and positioning. Lung shielding was necessary on the HM3 and some alterations had to be made to the gantry to accommodate children (Nijman *et al.*, 1989).

A second generation lithotripter (Siemens Lithostar) using X-ray localisation has been used in this unit for the primary treatment of renal stones *in situ*. We report our preliminary results on the treatment of renal calculi in children.

Patients and Methods

Fifteen children (8 male and 7 female) were treated for renal calculi in 17 renoureteric units between April 1988 and April 1990 on the Siemens Lithostar. Two children had bilateral stones and 1 of them had stones in the upper and lower moieties. The shock wave is produced by electromagnetic generation of a high voltage current pulsed through a coil

in the base of the shock head. This produces a magnetic field which repels an adjacent metal membrane, thus initiating a high pressure wave which is transformed into a shock wave as it travels through de-gassed water. This wave is focused by an acoustic lens, creating a high intensity focal zone. The total energy per pulse and the width of the high intensity focal zone in the Siemens Lithostar are intermediate between the spark-gap and the piezoelectric systems (Coleman and Saunders, 1989). The shock wave generator setting for the Lithostar is a voltage value (kV) with high voltage settings producing the highest peak pressures. The localisation system for the Lithostar is via 2 X-ray tubes—antero-posterior and 40° oblique providing accurate localisation for radio-opaque calculi.

The age of the patients ranged from 18 months to 15 years (average 9.4 years). All children were treated as in-patients. The total hospital stay ranged from 2 to 18 days (average 2.24). One child had undergone surgery on the same kidney which was to be treated for stone. One spina bifida child with bilateral ureterostomies was treated for bilateral staghorn calculi. Two children had unilateral megaureter and 1 child had previously undergone a ureteric reimplantation. Two children had infected urine and were on antibiotic treatment at the time of referral. Metabolic abnormalities included renal tubular acidosis in 1 child and idiopathic hypercalciuria in 2. One child had a radiolucent calculus and a ureteric stent. Left retrograde pyelography was performed via the stent to visualise the radiolucent stone which was then treated.

Prior to referral for ESWL, all children underwent intravenous urography and blood tests for renal function and a stone profile. Three children had ureteric stents *in situ* on referral and 1 child had a stent inserted before ESWL because of a large stone load. Stone size ranged from 5 mm in the longest diameter to a complete staghorn 40 mm in the longest diameter.

All patients were treated under a general anaesthetic. The first treatment of a 14-year-old girl was

attempted under sedation but this was abandoned because of pain and repeated at a later date under a general anaesthetic.

Results

Fifteen children with 18 stones in 17 renoureteric units were treated. Table 1 shows the number of stones and the sizes in each category. Stone size ranged from 5 to 40 mm in the longest diameter. Stone volume (as measured by multiplying the longest 2 diameters) varied from 25 to 200 mm² (average 55).

Table 1 Number of Stones and Sizes in each Category

Site	No.	Size (mm)
Pelvis	5	5–20
Upper calix	3	5–10
Lower calix	4	6–8
Simple staghorn	2	20–30
Complete staghorn	4	20–40
Total	18 stones in 15 children	

Table 2 shows the number of treatments and number of shocks for each category. The number of shocks per patient ranged from 1200 to 30,600 for a complex staghorn. The average number of shocks per treatment for all 3 categories was 4624. The number of treatments for any one stone ranged from 1 to 6 (average 1.42). Total treatment time ranged from 75 to 536 min. Time on table per session ranged from 45 to 105 min (average 74).

Table 3 shows the number of patients who were stone-free 3 months after ESWL. The 3-month follow-up was available by examining the X-rays. We defined stone-free as complete absence of fragments on a plain abdominal X-ray or an intravenous urogram for radiolucent stones. Complete clearance of the stone was achieved in 65% of all renoureteric units. Five children had residual calculi, with 1 of them having 2 residual fragments.

Table 2 Number of Treatments and Number of Shocks for each Category

Site	No. of treatments	No. of shocks
Pelvis	1–3	2000–17400
Upper calix	2–3	1200–18000
Lower calix	1–2	4000–6258
Simple staghorn	2–3	9000–12800
Complete staghorn	2–6	9733–30600

Table 3 Results after 3 Months

Status	No. of renoureteric units
Stone-free	11
Fragments < 2 mm	3
Fragments 2–5 mm	3

Fifteen children with calculi in 17 renoureteric units (2 bilateral)

Discussion

Extracorporeal shock wave lithotripsy has been established as an effective modality for the management of renal calculi in adults. In this study, the 3-month stone clearance rate was 65%, with 30% of patients requiring only 1 treatment. Of the 5 children who were left with residual fragments, 1 had a nephrolithotomy and 4 are still being observed. Since there is no place for simple observation of children with renal calculi (Williams and Johnston, 1982), the 4 children with residual stones would have to have further ESWL, percutaneous nephrolithotomy or open surgery.

Complications were minor and infrequent on the Lithostar. Three children with severe renal colic required analgesia and 1 child had a stent insertion for obstruction. This low complication rate is significant since endo-urological procedures on children have their limitations owing to paediatric patient size.

The Lithostar proved to be an effective second generation lithotripter for ESWL of renal calculi in children. There were no problems with patient positioning where cushions and padding were used. Since the focal zone is 60 × 11 mm, there was no need for lung shielding from the shock waves. X-ray shielding also presented no problems. One girl had a lower caliceal stone treated with ESWL and a lower ureteric stone removed ureteroscopically in view of the theoretical risk of ovarian damage due to radiation and/or the shock waves. However, there has been no evidence of mutagenic effects of ESWL *in utero* (Mendoza *et al.*, 1991).

Although the series is too small for definite conclusions to be drawn, the ultimate stone-free rate was not related to the initial stone size but rather to the machine setting. Higher kV settings were associated with a higher percentage of stone-free cases.

In conclusion, extracorporeal shock wave lithotripsy is a safe and effective primary treatment modality for renal calculi in children, with a reasonable success rate and minimal complications in the short term. Open surgery still remains the first treatment of choice in some centres for large staghorn calculi (Wilbert *et al.*, 1988). Using the Lithostar, general anaesthesia is required and radiation protection measures need to be taken. The small focal zone of the lithotripter makes lung shielding unnecessary. It is suggested that ^{99m}Tc-DMSA scans could be performed before and after a treatment course with ESWL in order to assess individual renal function until the long-term effects on the developing renal parenchyma have been fully evaluated.

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Surgery for Hypospadias Fistula

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Summary—The results of 12 years' experience in the surgical treatment of hypospadias fistula are presented. Overall, there was a success rate of approximately 50% for each attempt at surgical closure of a fistula. The chances of success were not significantly influenced by the number of previous surgical procedures. The best results were obtained with fistulae on the shaft of the penis which were closed with mucosal inversion and advancement of a skin flap over the fistula.

Fistula formation is the commonest complication of hypospadias repair, with a reported incidence of 10 to 15% for all forms of hypospadias (Duckett, 1986).

Several factors appear to be important in the development of a fistula. These include distal obstruction, loss of vascularity to the neourethra, use of non-absorbable sutures, poor suture technique, crossing and overlying suture lines, infection and extravasation of urine. However, there are occasions when, despite meticulous care and attention, with strict adherence to all the principles outlined above, a fistula appears in the post-operative period.

It is not our intention to analyse the causes of fistula formation, but rather to describe our experience in the surgical treatment of hypospadias fistula over the past 12 years.

Patients and Methods

A total of 48 boys underwent surgery for hypospadias fistula in this department over the past 12 years (1979–1981). The median age at the time of the first attempt at fistula closure was 55 months (range 15–192). Sixteen boys had undergone primary hypospadias surgery at another hospital and 9 of these had undergone between 1 and 6

unsuccessful attempts at fistula closure prior to referral to this department. The median delay between the primary hypospadias operation and the first attempt at repair was 11 months (range 2 weeks–48 months). The initial hypospadias repair performed in these boys is shown in Table 1. In most cases, details of the previous attempts at fistula closure were not available to us.

Although 7 of the fistulae were coronal, the majority ($n=39$) were found on the shaft of the penis. In 2 boys there were multiple fistulae.

Surgery was performed with a tourniquet (as required) and with the aid of optical magnification ($\times 3$). The distal urethra was examined for narrowing by the passage of urethral sounds. If distal narrowing was present, either dilatation or urethrotomy was performed and fistula closure was delayed for at least 3 months. The size and position of the meatus was assessed, together with the quality of the supporting tissues of the distal urethra.

Finally the fistula itself was examined. Usually this presented few problems, but on occasions the fistula was tiny and difficult to locate. A useful manoeuvre under these circumstances was to inject

Table 1 Primary Hypospadias Repair

Procedure	No.
Pedicled preputial tube graft (Duckett procedure)	18
Other 1-stage procedures (e.g. Mathieu, Magpi, flip-flap)	16
Two-stage repairs	14

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sterile saline into the urethral meatus with a 20-ml syringe while compressing the bulbar urethra. Using this technique it was always possible to visualise even the smallest fistula. This technique can also be of value in testing the repair after closure of the fistula.

A catheter (4-6 F infant feeding tube) was inserted throughout the operation to aid identification of the urethra. In all cases absorbable sutures were used for closure. In the early years of this review 6/0 catgut was the usual suture, but latterly we have used 6/0 vicryl.

In 8 boys with small fistulae (<2 mm diameter) either in the corona or on the shaft of the penis, closure was attempted by simple freshening of the edges, excision of the fistula and closure with inversion of the mucosa. The repair was in 2 layers and care was taken to avoid narrowing of the urethra. Every attempt was made to separate the suture lines, but inevitably they were usually closely apposed. Often these fistulae were noted early in the post-operative course and 4 closures were attempted within 3 months of the primary operation. Neither a urethral nor a suprapubic catheter was used in these cases.

In 28 boys a small or moderately sized fistula was found; this was usually on the shaft of the penis and was associated with a wide and healthy distal urethra. Some form of skin advancement procedure was performed in these boys. The fistula track was excised and then closed with a continuous suture and with mucosal inversion. Care was taken to avoid narrowing of the urethra. Adjacent excess healthy skin was then advanced over the fistula using a simple advancement flap or a Y-V plasty (Figs 1 and 2) and the closure was completed in 2 or 3 layers. If the excess skin was some distance away from the fistula, a rotation flap was performed (Fig. 3). If possible, additional support was provided by a layer of interrupted subcutaneous supporting sutures. For larger fistulae a urethral and/or a suprapubic catheter was inserted for 7 to 14 days.

In a further 5 boys there was a large fistula on the shaft of the penis, although the distal urethra was of adequate calibre. In these boys a repair similar to the Johanson second-stage urethroplasty was performed (Fig. 4). Again, care was taken to ensure mucosal inversion, with a 2- or 3-layered closure and with asymmetric suture lines. A urethral catheter was invariably used for 7 to 14 days post-operatively and in 2 cases this was supplemented with a suprapubic catheter.

In 6 boys the fistula was associated either with

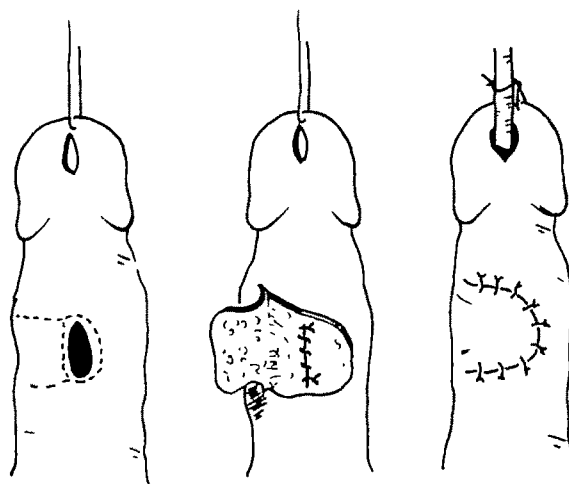


Fig. 1 Simple advancement flap

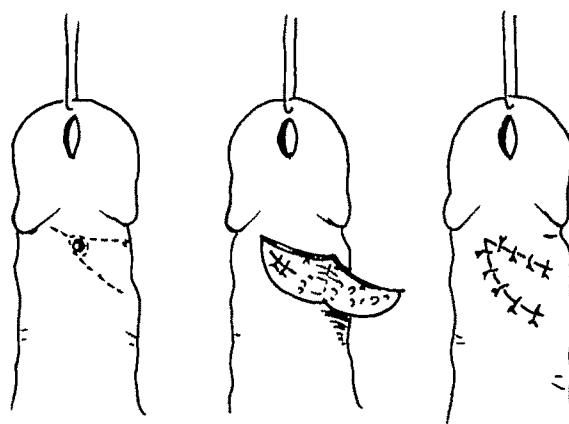


Fig. 2 Y-V advancement flap.

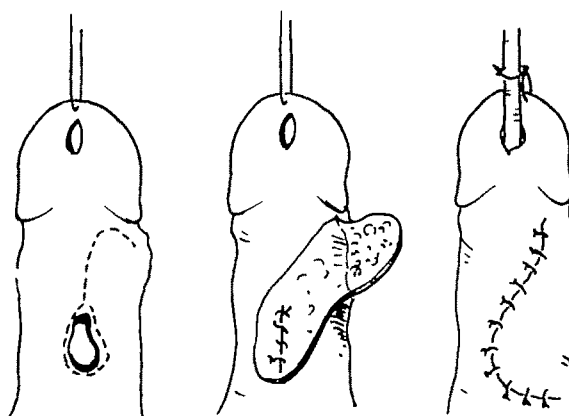


Fig. 3 Rotation flap.

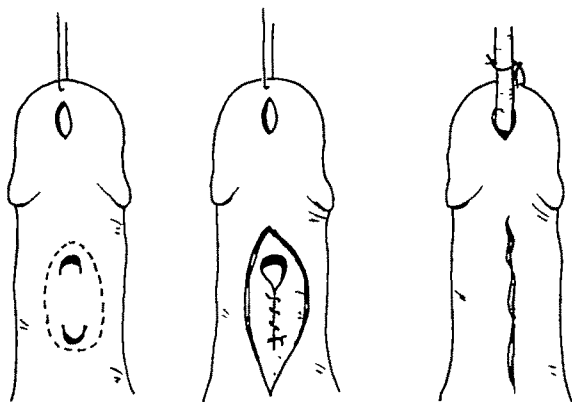


Fig. 4 Second-stage urethroplasty

severe distal narrowing, or with a proximally placed meatus or with poor tissue support for the distal urethra. In these cases a revision of the hypospadias repair was performed. If the urethral plate was adequate ($n=4$), a pedicled onlay graft of penile or preputial skin was used to provide the floor of the neourethra. In the other 2 patients a pedicled tube graft of preputial skin was used. In all cases both a urethral and a suprapubic catheter were left *in situ* for 7 to 14 days.

When extensive repairs were performed, foam dressings were used (Whitaker and Dennis, 1987).

Results

Distal obstruction

Four fistulae were associated with a narrow distal urethra and 3 of these were initially treated by dilatation. Subsequently, 1 fistula closed spontaneously and there has been no recurrence. The other 2 patients went on to have an advancement flap repair of the fistula. In the fourth case the distal stricture was associated with a large fistula. The distal urethra was laid open and a revision of the hypospadias was performed with a pedicled onlay graft of penile skin raised to form the floor of the urethra.

Results of initial operation (Table 2)

All of the fistulae treated by simple closure recurred and required further surgery. The success rate for those fistulae treated by an advancement flap technique was 20/28 (71%). For those patients who underwent a "second-stage urethroplasty" repair, 2/5 healed and for those who underwent a "complex" repair 3/6 healed. This gave an overall success rate of 25/47 (53%).

Table 2 Results of First Attempt at Fistula Closure

Operative technique	No.	Successful	%
Simple closure	8	0	0
Advancement flap	28	20	71
Second-stage urethroplasty	5	2	40
Complex repairs	6	3	50
Overall	47	25	53

Of the 9 patients who had undergone fistula surgery elsewhere, 6 (67%) underwent successful closure at the first attempt. This compares with 20 (51%) successful closures in the 39 boys who had not undergone previous fistula surgery.

Results of subsequent operations

Overall, 22/47 fistulae (47%) recurred after the initial surgical procedure. These boys went on to have further attempts at fistula closure using techniques similar to those outlined above. The results of subsequent operations are shown in Figure 5. Overall, the techniques used were either simple closure ($n=7$), of which only 1 was successful, and an advancement flap technique ($n=26$), of which 14 were successful.

At each successive operation approximately 50% of the fistulae were successfully closed, regardless of the number of unsuccessful operations which had been performed previously.

Timing of surgery

We attempted closure on 6 fistulae within 3 months of the primary hypospadias procedure. All but 1 were unsuccessful.

Use of catheters

At the first attempt at fistula closure, suprapubic catheters were used in 11 cases and the fistula recurred on 9 occasions. Urethral catheters were used in 28 boys and the fistula was successfully closed in 14 of them. No catheter was used in 15 boys and the fistula was successfully closed in 10.

Discussion

Spontaneous closure of hypospadias fistulae has been reported, and indeed some authors have recommended a variety of measures to encourage this. These include the use of adhesive tape to pull the fistula edges together and the use of topical silver nitrate in the early post-operative period if a fistula does appear (Horton *et al.*, 1980). In our experience these measures are of little value,

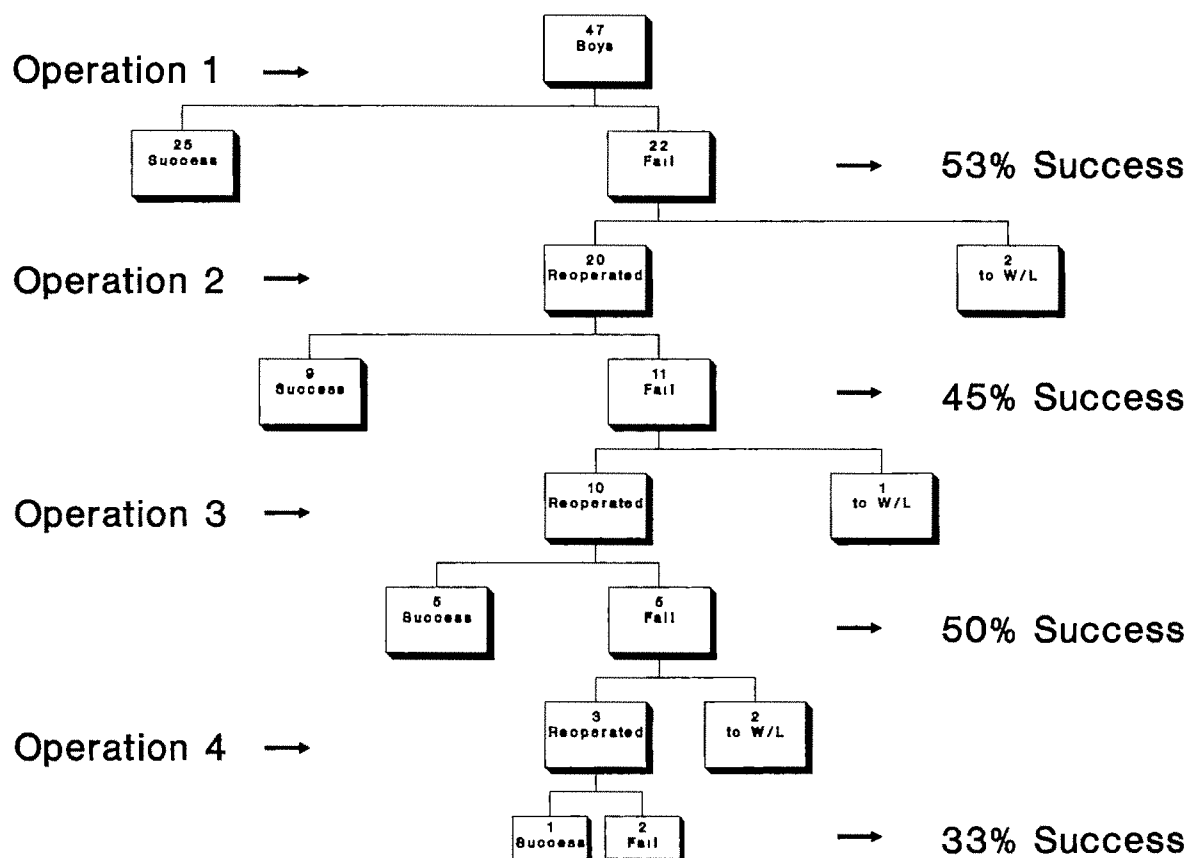


Fig. 5 Results of subsequent attempts at surgical closure.

although it is our anecdotal experience that occasionally there is a history suggestive of spontaneous fistula closure. The only documented spontaneous closure in this series followed dilatation of a distal stricture and clearly the identification of distal narrowing is one of the priorities of fistula management.

Surgery for hypospadias fistula is notorious for its high failure rate (Duckett, 1986) and this is borne out by our results. However, a review of the literature reveals several authors who have claimed excellent success rates for specific operative techniques. For instance, Goldstein and Hensle (1981) reported successful closure in all of their patients treated using a technique whereby the urethra and skin were closed at right angles to each other. Saad *et al.* (1980) reported a similar success rate for 12 boys in whom a Y-V advancement flap was used, and Moscona *et al.* (1984) found a similar technique to be successful in 22/24 boys. Roberts (1982) described a rotation flap technique for fistula closure, with a successful result in 17/18 boys.

Geltzeiler and Belman (1984) described the use of a de-epithelialised "pants over vest" technique, with success in 19 boys with a mid-shaft fistula. Duckett (1986), however, suggested that extensive mobilisation was unnecessary and reported a cure in 29/32 boys treated by a technique remarkably similar to our "simple" closure technique. In our hands this technique has not been successful and we would suggest that this probably relates to the close proximity of the suture lines.

Overall, our results compare badly with many of those in the series described above. This is possibly due, in part, to patient selection, since some of the previous reports were clearly limited to simple fistulae on the shaft of the penis. Our results reflect experience with a whole range of hypospadias fistulae and are similar to those obtained by Zagula and Braren (1983). From examination of both their results and ours, it is clear that hypospadias fistulae can be divided into 2 groups:

(1) Those small fistulae (usually on the shaft of the penis) which are associated with an otherwise

good result from the primary hypospadias surgery. Using skin advancement techniques, approximately 70% of these fistulae will be cured by the first operation.

(2) Large fistulae, coronal fistulae and those associated with a poor result from the initial hypospadias repair. In these patients the results of closure are (as might be expected) less good.

The use of catheters has excited a great deal of controversy in previous reports. Our practice has been to use diversion for the more complex and difficult repairs. This probably explains the similarity in success rates in our series between those boys who had a urethral catheter (with or without additional suprapubic diversion) and those who did not.

We found that the number of previous procedures which the boy had undergone did not adversely influence the results of subsequent attempts at closure. This is perhaps surprising, since it might be expected that repeated surgery would result in increased scarring and poor vascularity. To this end, we feel, in common with Horton and Horton (1988) that a delay of at least 6 months is needed to minimise the inflammation and induration of the penile skin and urethra.

We would therefore make several recommendations to anyone attempting hypospadias fistula repair. Firstly, the operation should be delayed for at least 6 months from the time of primary surgery. This will give time for inflammation and induration to resolve, thereby facilitating the subsequent surgical procedure. Distal obstruction must be actively sought and treated prior to fistula closure. For small fistulae on the shaft of the penis we recommend excision of the fistulous track with inversion of the mucosa by a continuous watertight closure. Some form of skin advancement technique is then needed to cover this track. The presence and location of the excess healthy skin which is to be used for coverage of the fistula will determine the exact surgical technique which is to be used in any particular case. Adequate mobilisation is mandatory to avoid any tension in the repair, and overlapping suture lines are to be avoided. For larger fistulae and those associated with other complications of hypospadias repair, more extensive reconstructive procedures are required which inevitably have a greater chance of failure. Finally, we feel that urinary diversion should be reserved for those fistulae which are complex or difficult to close.

We have found the surgery of hypospadias fistula to be both challenging and, on many occasions, disappointing. What may appear to be a perfectly adequate repair will occasionally break down. We do feel that attention to the details of surgical technique will improve the results of fistula surgery. However, in our hands, almost 50% of the boys required at least 2 surgical procedures to close their fistula.

It may be that the introduction of newer surgical techniques, such as the use of bladder mucosa (Keating *et al.*, 1990) or tissue glues (Lerner and Binur, 1990), may prove to be an advance. The results of such techniques are awaited with interest.

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Fixation of a Single Testis: Always, Sometimes or Never

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Summary—If it is necessary to perform an orchiectomy for an intravaginal testicular torsion it is the usual practice of surgeons to fix the contralateral testis. When faced with a child with only one testis for another reason it is our practice to fix this single testis to eliminate the small but disastrous risk of a torsion. We were interested to see whether this practice was usual and therefore sent out a questionnaire to the 67 consultant paediatric surgeons and urologists in Great Britain. Sixty-six surgeons replied. Seven surgeons (11%) always fix the single testis, 28 (42%) sometimes and 31 (47%) never fix a single testis. Five surgeons had looked after 6 patients who had a torsion of a second unfixed testis after losing the first for a reason other than intravaginal torsion. Four of these patients had initially had a neonatal supravaginal torsion, 1 had a torsion of an undescended testis and the sixth had severe testicular atrophy following an inguinal herniotomy.

In our opinion the devastating loss of these solitary testes makes contralateral testicular fixation after an orchiectomy for whatever reason mandatory.

Delaseuve first described a torsion of the testis in 1940. The abnormal insertion of the tunica vaginalis in association with the bell-clapper deformity of the testis, which is usually bilateral, has led to the philosophy that fixation of a contralateral testis following an intravaginal torsion is mandatory and this is agreed by all surgeons (Williamson, 1976). If the first testis is lost for another reason, *e.g.* neonatal supravaginal torsion, failed orchiopexy or orchiectomy for tumour, there has been little agreement on the correct management of the contralateral testis. We have tried to ascertain the current clinical practice in this country and whether there is any significant risk to a single unfixed testis in this situation.

Methods

A questionnaire (Fig.) was sent to the 67 paediatric surgeons and urologists in the United Kingdom together with a covering letter.

Read at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

Results

Fifty-five surgeons initially replied. The remaining 12 were sent a gentle reminder and a further 11 replied. One surgeon had left the country, thus giving a 98% response rate. Seven surgeons always fix a single testis, 28 sometimes and 31 never fix a single testis unless the initial testicular loss was due to an intravaginal torsion. The reasons for fixation in the "sometimes" group were varied (Table). Five surgeons had encountered 6 patients who had had a torsion of their unfixed testis. The reasons for initial testicular loss were neonatal torsion (4

Table Reasons for Testicular Fixation by Surgeons who "Sometimes" Fix a Single Testis

(a) Congenital monorchia	13
(b) Dysgenetic testis/failed orchiopexy	7
(a) and (b)	1
(b) and (c)	1
(c) Contralateral hernia with atrophy	2
(d) Horizontal lie $\pm$ pain	4
Total	28

Name:—

Hospital:—

Specialty:— General Paediatric Surgeon ☐
 General Paediatric Surgeon with
 a major interest in Urology ☐
 Paediatric Urologist ☐

- (1) Apart from fixation of the contralateral testis in torsion, do you otherwise fix a single testis?

Always ☐
 Sometimes ☐
 Never ☐

- (2) If the answer to (1) is sometimes, do you fix the remaining testis for?

a) Congenital monorchia ☐
 b) Unilateral orchidectomy for dysgenetic testis or failed orchidopexy ☐
 c) Unilateral orchidectomy for tumour ☐
 d) Other—please specify—

- (3) a) Have you ever had a patient who presented with torsion of a single testis?

☐ YES ☐ NO

- b) If yes to 3 a) can you remember the reason for the monorchia—please specify.—

- (4) How do you fix the single testis?

Please specify Jaboulay procedure, absorbable or nonabsorbable sutures, the method of fixation, Dartos pouch etc

Fig.

patients), torsion of an undescended testis (1) and testicular atrophy following an inguinal herniotomy (1).

The methods of fixation varied from surgeon to surgeon. The majority used a dartos pouch technique.

Discussion

As in the majority of controversies in surgery, there was no unanimity regarding the question of fixation of a single testis among surgeons except following an intravaginal postnatal torsion. In this condition the high insertion of the tunica vaginalis and bell-clapper deformity are found bilaterally (Lyon, 1961) and between 5 and 30% of contralateral testes not fixed will subsequently undergo torsion (Abeshouse, 1963). If a testis is single for another reason we have little information regarding the risks of

torsion. Harris *et al.* (1982) described a bell-clapper deformity in 13 patients following negative explorations for unilateral cryptorchidism. Bellinger (1985) confirmed an abnormal testicular fixation in 5 of 6 contralateral testes explored following the diagnosis of monorchia. Both of these authors recommended fixation of the contralateral testis in congenital monorchia.

Most neonatal torsions occur in the perinatal period, *i.e.* in the few days before or after birth, and the majority of these torsions are extravaginal (Das and Singer, 1990). A testis undergoes extravaginal torsion because its attachment to the scrotal wall in the neonate is still flimsy, and torsion is not due to an abnormality of the insertion of the tunica vaginalis. Therefore it can be argued that in these patients the risks of a contralateral torsion are remote. However, LaQuaglia *et al.* (1987) reported 4 cases of bilateral neonatal torsions of which 2 were asynchronous and 1 patient was rendered anorchic. We have also seen one unreported case of an asynchronous bilateral neonatal torsion in which the second testis was saved by an urgent exploration.

There therefore appear to be risks to those patients born with monorchia and in those who suffer a neonatal torsion. The risks of losing a second testis are admittedly small and there are few case reports in the literature. This survey of paediatric surgeons and urologists in the United Kingdom revealed 6 patients who lost a single unfixed testis for 3 different reasons, the most common being neonatal torsion. As anorchia is such a disaster, we suggest that the risks of this catastrophe outweigh the minimal risk to the patient of an anaesthetic and testicular fixation.

Various methods of fixation are used by surgeons. There have been many reports of torsion occurring after previous testicular fixation (May and Thomas, 1980; Vorstman and Rothwell, 1982; Thurston and Whitaker, 1983). It has been suggested that the use of a non-absorbable rather than an absorbable suture will prevent this complication (Tawil and Gregory, 1984). The recent experimental work by Bellinger *et al.* (1989) showed that, in the rat, suture fixation led to local testicular damage and only partial adherence between the testis and the tunica vaginalis and scrotal wall. Placement in a dartos pouch led to complete circumferential adherence of the testis to the dartos muscle. This work confirmed our clinical belief that sutureless fixation in a dartos pouch is both safe and effective. All patients with a single testis should, in our view, have it fixed in this way.

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Delayed Linear Growth in Children with Enterocystoplasties

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Summary—A series of 60 children whose urine was stored in pouches formed in whole or in part from bowel were reviewed to establish the effect on growth in height and weight. The mean age at operation was 7.8 years (range 0.9–14.1). Patients were included only if there were at least 2 measurements of both parameters pre-operatively and 2 post-operatively over a minimum follow-up of 2.5 years. Delayed growth in height alone occurred in 12 children (20%), with a mean loss of 25 percentile points (range 10–50). Delayed growth in height and weight occurred in 4. Accelerated growth in height alone, weight alone and in both occurred in 2, 7 and 7 respectively. There was no difference in a wide range of laboratory data between any of these groups.

Although changes in growth rate (for better or worse) may occur for a variety of reasons after major surgery, delayed linear growth in isolation is an unusual and worrying finding that suggests a major alteration in bone development.

Segments of intestine have been used in lower urinary tract reconstruction for many years, but only in the last decade have large numbers of patients been treated. Many different types of reconstruction are now available, ranging from a modest augmentation cystoplasty to a complete reconstruction by continent diversion. The common element in all is the use of a segment of intestine to form a part or the whole of the reservoir. Some anxiety has been expressed by surgeons regarding the metabolic complications that might ensue. Would the reservoirs behave as conduits with relatively minor consequences, or in a manner similar to the ureterosigmoidostomy with major metabolic problems, or in a different and unpredictable way?

Our protocol for follow-up of children and adults has been reported by Wagstaff *et al.* (1991). It was designed to cover the predictable and some of the unpredictable complications that might be encountered. We found a high incidence of metabolic and infective complications. Unfortunately, measure-

ment of height and weight were not included in routine follow-up. In 60 of 106 children, however, both height and weight were measured on at least 2 occasions before and 2 after reconstruction. A review of these results provides interesting data.

Patients and Methods

All 183 patients whose urine was stored in reservoirs formed in whole or in part from bowel under the care of our paediatric and adolescent unit have been documented. For the last 2 years the follow-up protocol that had been loosely used has been followed prospectively. From the stored information we have retrieved data on the haematological and biochemical profiles and infection patterns of the patients. All types of bowel and all patients were considered and the results have been reported by Wagstaff *et al.* (1991).

There were 106 children in the group. Of these, 60 happened to have had both height and weight measured on at least 2 occasions pre-operatively (over 2 years except for the youngest patients) and post-operatively (over a minimum follow-up of 2.5

years). Heights and weights were plotted on standard percentile charts for English children (Fig.).

In many children the measurements had been made less often and so they were not included in this survey. On retrospective review it was not possible to say why some patients had been measured and others had not, but no special reasons were identified. Patients in end-stage renal failure and those with limb abnormalities from myelomeningocele were excluded.

The 15 patients who showed delayed linear growth were of particular interest and were compared with all of the other patients to see if there were any differences in the laboratory data.

The original diagnoses of the patients are shown in Table 1 and the segments of bowel used in Table 2.

Results

The outcome for growth in height and weight derived from the percentile growth charts is shown in Table 3. The most significant finding was delay

Table 1 Original Diagnosis in 60 Patients

Diagnosis	No.
Exstrophy/epispadias	45
Neuropathic bladder	9
Trauma	1
Various others	5

Table 2 Bowel Segments used in Reconstruction

Bowel segment	No.
Colon	45
Ileum	9
Mixed	6

Table 3 Summary of Growth Results in 60 Patients with Lower Urinary Tract Reconstructions including Bowel Segments

		Weight percentile		
		Up	Steady	Down
Height percentile	Up	7	2	—
	Steady	7	23	2
	Down	3	12	4

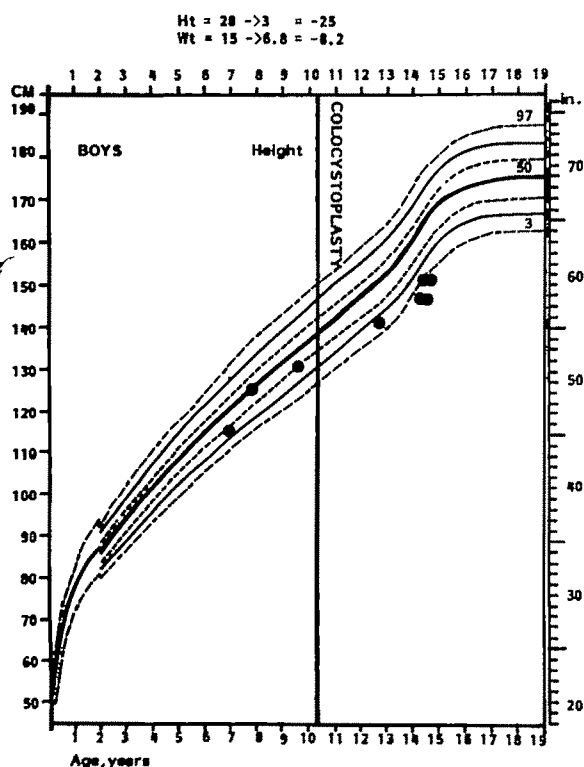


Fig. Height percentile chart for patient with lower urinary tract reconstruction showing delayed linear growth.

in linear growth while growth in weight was maintained; this occurred in 12 patients (20%). Three further patients had delayed linear growth with increased growth in weight, making a total of 15. A typical percentile growth chart is shown in the Figure.

The mean loss in linear growth for the 12 patients losing height alone was 28 percentile points (range 10–50).

When the patients' details and laboratory results were reviewed (Tables 4–6) it was seen that there were no substantial differences between the 15 with delayed linear growth and all of the other patients, except that the delay was slightly less common in those with ileal pouches.

One of the 15 patients with delayed linear growth had a major post-operative complication, compared with 3 of the other 45 patients.

Discussion

Some of the consequences of storing urine in a reservoir made in whole or in part from bowel

Table 4 Growth Results in Relation to Original Diagnosis

Diagnosis	Delayed linear growth (%) (n=15)	All other patients (%) (n=45)
Exstrophy	67	78
Neuropathy	33	9
Trauma	—	2
Other	—	11
Total	100	100

Table 5 Growth Results in Relation to Bowel Segment used for Lower Urinary Tract Reconstruction

Segment	Delayed linear growth (%) (n=15)	All other patients (%) (n=45)
Colon	67	78
Ileum	6	18
Mixed	27	4
Total	100	100

Table 6 Percentage of Patients with and without Delayed Linear Growth who had Abnormal Laboratory Results

Result	Delayed linear growth (%) (n=15)	All other patients (%) (n=45)
Anaemia	7	20
Definite HCA	20	31
Borderline HCA	27	31
Troublesome UTI	7	11
Occasional UTI*	20	23
Stones	13	9

HCA = Hyperchloraemic acidosis defined as plasma bicarbonate <18 mmol/l and chloride >108 mmol/l on at least 2 occasions. Borderline HCA defined as occasional abnormality in both results or consistent abnormality in one. UTI = Urinary tract infection. * Includes asymptomatic bacteriuria in more than 50% of specimens.

might be predicted from experience with conduits and ureterosigmoidostomies. We designed our follow-up protocol to detect these and also some unpredictable complications. In our study of the whole group of 183 children and adolescents we found anaemia in 8.2% (none macrocytic), definite hyperchloraemic acidosis (HCA) in 13.7% and

borderline HCA in a further 21.9%, significant urine infection in 27.9% and reservoir stones in 12% (Wagstaff *et al.*, 1991). The biochemical findings were broadly in line with those of Nurse and Mundy (1989) and the haematological findings with those of Canning *et al.* (1989).

The effects on growth were unexpected and a chance finding. In any retrospective review it is possible that the results are artefactual. For example, not all patients were measured. Those who were measured may have been selected because of parental comment about unusual growth patterns. The measurements, taken for no very good reason, might have been inaccurate: it is particularly difficult to measure height and many children are found to be taller than casual measurement suggests. Since our data were assembled, 29 children have been seen and re-measured. In no case did the new measurement alter the child's position on the percentile chart, suggesting that earlier measurements were accurate.

It is not unreasonable to assume that, in the past, patients were randomly selected for measurement and that there was a random distribution of errors throughout the group before and after surgery. Many of the measurements were made for nuclear medicine studies of glomerular filtration rate, which requires particular accuracy.

Changes in both height and weight growth rates after surgery are understandable. Children who are ill may be made better by surgery and catching up in growth then occurs. Although lower urinary tract reconstruction is often a cosmetic procedure, many children are reconstructed because of deteriorating renal function or chronic infection. Increased weight and height together (seen in 7 patients) may be the result of better general health. Conversely, delayed growth may be caused by the general upset of major surgery. In addition, patients may have constitutional delays in their growth spurts unconnected with any illness.

It is more difficult to account for changes in one parameter alone. The worrying finding in this survey was the loss of linear growth alone in 20% of patients, and its scale. The mean loss was 25 percentile points on the growth chart, with 1 patient losing 50 points. It is difficult to dismiss changes on this scale as due to incorrect measurement or patient selection. Even if patient selection were a factor, it is still the case that those selected had delayed linear growth.

Assuming that the observation is valid, the laboratory parameters that we have measured routinely do not offer an explanation. It is likely

that, if there is a specific cause, it lies in the metabolism and maturation of bone.

Bone demineralisation and osteomalacia are recognised complications of HCA, but clinical problems and radiological abnormalities are not seen until the condition is far advanced (Harrison, 1958). Impaired growth was not recorded as a complication of ureterosigmoidostomy in a meticulous review of 1673 patients (of all ages) followed up for 10 years, although the appropriate measurements may not have been made (Jacobs and Barr-Stirling, 1952).

In experimental young rats with ureterosigmoidostomies, those with corrected HCA grew more quickly and achieved a greater weight at the time of sacrifice than those without correction (Imler *et al.*, 1979). However, in a similar experiment, McDougal *et al.* (1988) found that continuous prophylactic antibiotics allowed even those with uncorrected HCA to grow normally. These observations were on overall growth and not length alone; nonetheless, they illustrate that there is a theoretical potential for the storage of urine in bowel to affect growth.

Although the incidence of HCA was the same in both groups, there may be subtle disturbances of acid/base balance that are not detected by conventional analysis of venous blood. Nurse and Mundy (1989) found that all patients with intestinal reservoirs had metabolic acidosis with respiratory compensation on blood gas analysis.

We have only recently started to carry out arterial blood gas analysis on our patients. In 29 patients, 17 were normal, 9 showed various minor deviations from normal and 3 showed marked acidosis. There was no difference between children with normal growth and those whose growth was delayed (unpublished data).

Previous reviews of diversion or lower tract reconstruction have not reported delayed growth in height. At present we can only speculate on the causes of the delay that we found. In the future patients must be accurately measured before and after surgery and investigations of bone growth must be done.

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Case Reports

Lymphangiography of Filarial Chyluria: Injections via Right and Left Feet at Different Times

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Case Report

A 69-year-old-female complained of intermittent milky urine in March 1979. Urine analysis showed chyluria. She had developed chyluria for the first time in 1969. Complete blood count and blood chemistry showed lymphocytopenia and hypoproteinaemia. Cystoscopy showed chyluria passing through the right ureteric orifice. The first lymphangiogram via the left foot showed a lymphaticorenal fistula on the right side. The second lymphangiogram via the right foot was performed 1 month later and showed again a lymphaticorenal fistula on the right side (Fig.); 9 ml of lipiodol ultra fluid were used as contrast medium in a bolus dose. There was no obstruction of the thoracic duct.

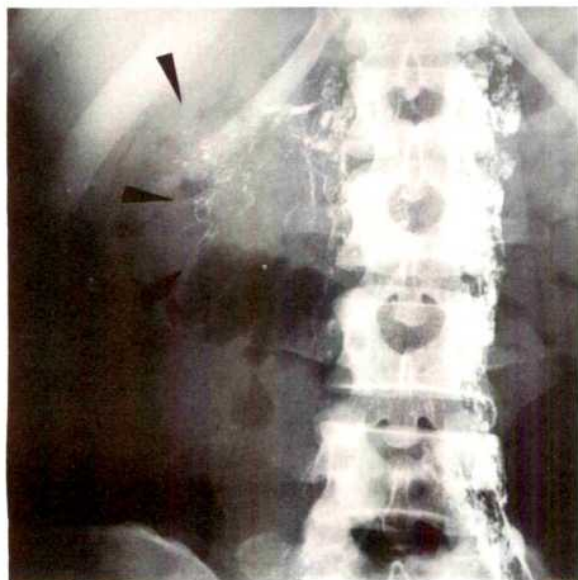


Fig. Second lymphangiogram via the right foot showing a right lymphaticorenal fistula. Contrast medium passed through crossover channels from left to right.

Comment

Kinmonth *et al.* (1955) reported pedal lymphangiography for the first time. This method helped to diagnose lymphaticorenal fistulas in patients with chyluria (Akisada and Tani, 1968). Lymphangiography of patients with chyluria showed characteristic findings such as lymphaticorenal fistula, dilatation, tortuosity and an increase in the number of lymphatic channels. Yamauchi (1983) claimed that crossover channels in the abdomino-aortic lymphatics were also characteristic of filarial chyluria. Lymphangiography has been performed via both feet at the same time. However, we performed it via the right and the left foot at different times and a lymphaticorenal fistula was seen on the same side. Contrast medium passed through the crossover channels from left to right. It seems that a disorder of the lymphatic valve caused by filariasis is responsible for these findings. Unilateral pedal lymphangiography is thought to be useful in identifying crossover channels and making a diagnosis in patients with chyluria.

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Delayed Presentation of Posterior Urethral Valves

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Patients with obstructing posterior urethral valves rarely present after the age of 10 years, but we report 2 such cases.

Case Reports

Case 1. A 12-year-old boy presented with a 6-month history of intermittent left renal colic. Micturating cystourethrography (MCU) revealed the typical findings of posterior urethral valves (Fig. 1).



Fig. 1 Voiding urethrogram revealing obstruction at the site of posterior urethral valves.



Fig. 2 Retrograde urethrogram revealing hypertrophy of the verumontanum.

Case 2. A 17-year-old male had a 3-month history of bladder outlet obstruction. The urethra was not visualised on the MCU as he was unable to void, but the bladder was trabeculated. Retrograde urethrography appeared normal apart from hypertrophy of the verumontanum (Fig. 2). In view of the bladder trabeculation an atypical obstructing lesion was suspected and urethroscopy revealed a posterior urethral valve arising from the lower part of the verumontanum.

Endoscopic fulguration was performed in both patients and they made an uneventful recovery.

Comment

Patients with posterior urethral valves usually present early in life, 22% at birth and 52% within the first 3 months (Scott, 1985). Few reports are available on late presentations (Marsden, 1969; Heaton *et al.*, 1989). Young children often present with obstruction and have a greater degree of renal impairment than older children, who tend to have infective problems (Marsden, 1969; Heaton *et al.*, 1989).

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Urethral Injury Secondary to Penile Strangulation by Hair

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Case Reports

Case 1. A 3-year-old circumcised boy presented with a penile fistula. Physical examination, performed under general anaesthesia, showed a marked ventral penile depression with a coil of hair strangulating the glans at the coronal sulcus. After local debridement and dissection of the urethral edges an end-to-end anastomosis was

carried out. A multiperforated silicone splint was kept in the distal urethra for 7 days and a suprapubic catheter was maintained until the patient regained normal micturition.

Case 2. A 14-year-old circumcised boy presented with a chronic urinary penile fistula. He had a history of enuresis. Physical examination revealed a circumferential subglanular loss of tissue in the penile shaft with complete section of the urethra (Fig.). A strand of hair was also found to encircle the penis at the groove. One week after section of the hair, an end-to-end anastomosis of the urethra was performed. The patient made a satisfactory recovery.

Comment

Penile constriction by a strand of hair is more likely to be encountered within socially disadvantaged young boys and its incidence is high in the Maghreb district (Abouloula *et al.*, 1980; Harouchi *et al.*, 1980).

It is frequently seen in boys who are neglected by their family or who are mentally retarded. In some cases it may be an attempt by ignorant parents to control urinary incontinence in their child (Sheinfeld *et al.*, 1985).

Continuous constriction by the hair leads to progressive transection of the penile structures. The damage ranges from local irritation to necrosis of the penile shaft. The lesions predominate on the

ventral side of the penis, since the corpus cavernosum is more resistant to section than the periurethral tissues. Urethrocuteaneous fistula constitutes an advanced stage of damage.

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Scrotal Bladder with Scrotal Calculi

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Scrotal calculi lying between the tunica and testes have been reported by Liukowski *et al.* (1985). They appear to originate as fibrinous deposits in the tunica vaginalis or as remnants of the appendix testis or appendix epididymis that have twisted and become mobile (Zuluaga *et al.*, 1987). Scrotal cystocele with multiple calculi has also been reported.

We present a case of multiple scrotal calculi secondary to a fistula between the urethra and scrotum.

Case Report

A 66-year-old man presented with enlargement of the right hemiscrotum and a long-standing history of urinary incontinence. Compression of the scrotum produced an immediate flow of urine.

The patient had had a transurethral resection of the prostate for carcinoma, urethral stricture dilatation using the Otis urethrotome and a Jabouley procedure for a left hydrocele 6 years previously. Post-operatively he had had a *Pseudomonas* and *Str. faecalis* urinary tract infection which was treated with gentamicin. Symptomatic bone metastases developed 3 months later and he underwent bilateral orchiectomy. Two years later further painful pelvic and left hip metastases were treated with radiotherapy, 300 cGy at mid-plane dose $\times$ 10 fractions. There was a complete radiological remission in his disease.



Fig.

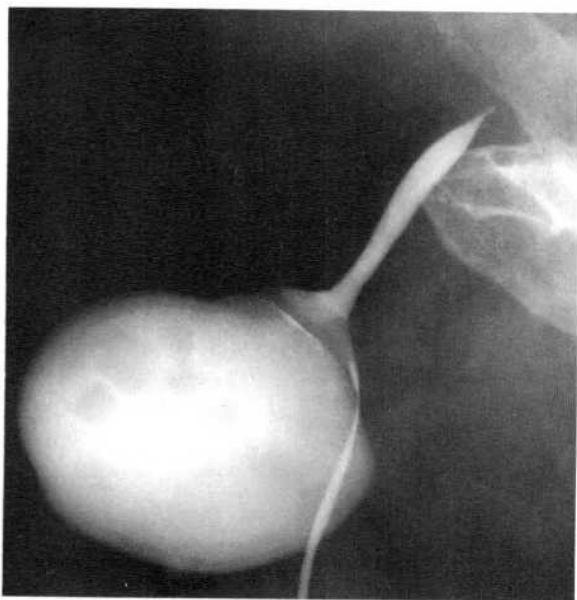


Fig. Urethrogram showing urethral fistula to scrotum with scrotal calculi.

Clinical examination on recent presentation revealed a cystic swelling in the right side of the scrotum with palpable calculi within it. An ultrasound scan confirmed the cystic structure with acoustic shadows suggesting stones. A plain X-ray showed calcified stones within the scrotum. An ascending urethrogram revealed a scrotal cavity communicating with the inferior part of the mid-urethra; the cavity contained 7 well defined radio-opaque calculi (Fig.).

At surgical exploration the scrotal sac was incised, numerous calculi were removed and the fistulous connection between the urethra and scrotal sac, which measured 2×0.5 cm, was closed in 2 layers.

The patient continued to have urinary incontinence but urine no longer collected within the scrotum. Urethrography revealed no evidence of urinary extravasation.

Comment

Chronic fistulas involving the adult male urethra are usually iatrogenic, arising after urethral or prostatic surgery, although some have inflammatory, traumatic or trophic causes (Blandy and Singh, 1972).

In this case there are several possible aetiological factors. Firstly, it is conceivable that a peri-urethral abscess developed following transurethral resection and urethrotomy.

Secondly, radiotherapy to the pelvis may have damaged the blood supply of the urethra. Thirdly,

the urethra may have been injured during urethral dilatation or transurethral resection of the prostate. Whatever the aetiology, this case supports the theory that stagnant urine within the scrotum may lead to calculi formation.

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Acute Urinary Retention Caused by Anterior Urethral Polyp

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Urethral polyps are rare and only 40 cases have been reported in the literature.

Case Report

A 29-year-old Turkish male was admitted to a peripheral hospital with acute retention of urine preceded by a 2-month history of dysuria and a poor stream. An attempt at urethral catheterisation had failed but urethral dilatation was successful and the patient was able to void urine. He complained of haematuria following this procedure and was referred to us. On examination there was a firm lump measuring 1 cm in the bulbar urethra; the rest of the examination was unremarkable. Urine microscopy revealed red blood cells and intravenous urography was normal. An ascending urethrogram showed a smooth filling defect at the level of the bulbar urethra (Fig.) and the contrast did not pass beyond that level. Micturating cystourethrography demonstrated the same defect. Cystourethroscopy revealed a 1-cm, sessile polyp occupying the entire lumen of the bulbar urethra. A 10 F paediatric cystoscope could be passed beyond it and the rest of the urethra and bladder were normal. A biopsy was taken



Fig. Ascending urethrogram showing filling defect in the bulbar urethra.

from the polyp, which was fulgurated in 2 sessions. Repeat cystoscopy 2 months later showed no evidence of recurrence but there was a stricture at the site of fulguration which required optical urethrotomy. Histologically the polyp was lined by 2 to 3 layers of transitional epithelium with fibrovascular stroma infiltrated by neutrophils.

Comment

Polyps of the urethra are rare and are usually congenital. They are more common in the posterior than the anterior urethra and patients present with obstructive symptoms (Miroglu *et al.*, 1988). Occasionally they occur in adults, when haematuria is the commonest symptom (Downs, 1970). The polyps are managed by transurethral resection in adults and by open excision in infants (Redman and Robinson, 1977). Recurrence has not been reported.

Anterior urethral polyps are usually single and only 1 case of multiple polyps has been reported (Moriya *et al.*, 1988).

The penile and bulbar urethra should be palpated in patients presenting with acute retention of urine or dysuria, particularly in young adults and children. An indurated area or a lump in the absence of radio-opaque stone on plain X-ray is suggestive of a stricture or (rarely) a polyp. Both can be diagnosed by urethrography and urethroscopy.

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Intraprostatic Stents—a New Complication

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The use of prostatic stents as an alternative to long-term catheterisation in patients who are at high risk from surgery is currently under evaluation. The intraprostatic spiral described by Fabian (1980), and later modified, has recently been employed with reasonably encouraging results (Harrison and De Souza, 1990; Nielsen *et al.*, 1990). Reasons for failure and removal of stents included recurrent dislocation, detrusor hypocontractility, urge incontinence and persistent urinary tract infection. We present a further complication.

Case Report

A 66-year-old man with multiple medical problems presented with urinary retention following a myocardial infarction. He was treated initially with an indwelling catheter and then underwent insertion of a Porges steel intraprostatic spiral (Fig. 1). His urine prior to operation was sterile. Following surgery he voided urine satisfactorily and was discharged home. Subsequent mid-stream specimens of urine 2, 3 and 6 months after insertion all showed relapsing infection with coliforms and he was treated with appropriate antibiotics. Seven months after insertion he developed symptoms of outflow obstruction requiring suprapubic catheterisation. At subsequent operation a calcified prostatic stent was removed and an adherent stone, which was protruding into the bladder, was crushed and removed (Fig. 2). Analysis showed this to consist of struvite. The stent was replaced with an expanding titanium stent of the type which usually undergoes epithelialisation.

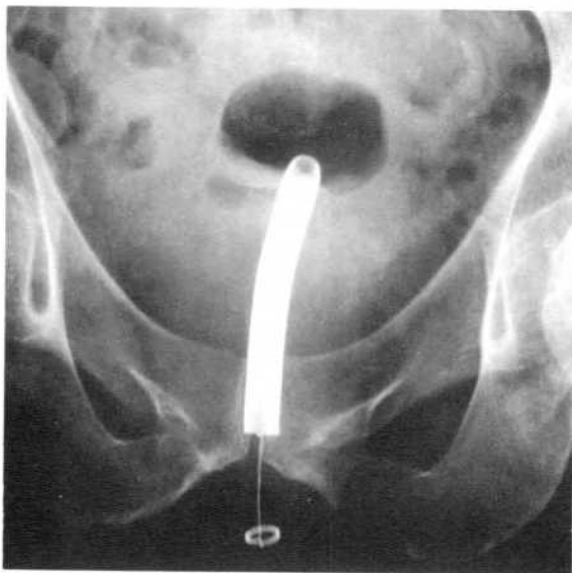


Fig. 1

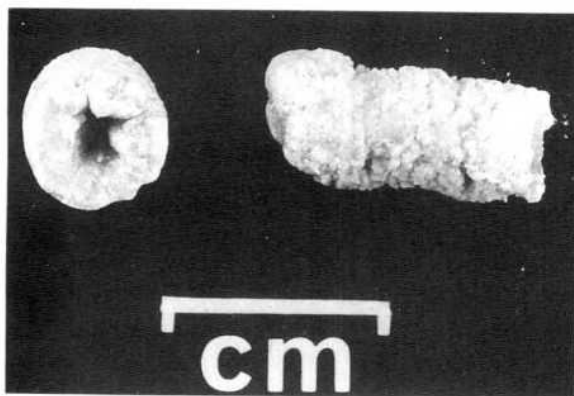


Fig. 2

Comment

The intravesical and intraprostatic portion of any prostatic stent provides a potential source of encrustation and stone formation. However, of the 75 stents studied by Harrison and De Souza (1990) and Nielsen *et al.* (1990), only 1 patient was reported as having minor encrustations, despite several patients having persistent bacteriuria.

Our case shows that encrustation may be a significant problem in the longer-term use of those stents which are not epithelialised. We suggest close follow-up, with those patients who exhibit persistent bacteriuria having their stents replaced by an

expanding stent which should eventually undergo complete epithelialisation.

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Intestinal Metaplasia of the Bladder: Implications for Management

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A wide spectrum of glandular metaplastic changes may be seen in the bladder. At one end spotty mucin production can be seen in individual cells and mucin-producing glandular epithelium can be seen in cystitis glandularis (CG). Such changes are common and of dubious significance. At the other extreme is extensive replacement of the urothelium with an epithelium resembling intestinal mucosa and containing specialised cells (Paneth cells and argentaffin cells). This complex glandular or intestinal metaplasia is recognised as a pre-malignant condition (Bullock *et al.*, 1987). As primary adenocarcinoma in the bladder carries a poor prognosis, with only 18% of patients surviving 5 years (Anderstrom *et al.*, 1983), the management of any pre-malignant finding is paramount. We describe a case of intestinal metaplasia and discuss the implications for management.

Case Report

A 59-year-old Caucasian male was investigated for haematuria. He gave a history of clot retention and difficulty in emptying his bladder. He smoked 40 cigarettes per day but denied any other relevant medical history. The IVU was normal. Cytology revealed numerous leucocytes but no epithelium was available for

cytodiagnosis. Culture of the urine grew *Ps. aeruginosa*. Cystoscopy revealed a necrotic-looking tumour on the right lateral wall of the bladder and biopsy showed actively inflamed colonic mucosa. Sigmoidoscopy revealed an adenomatous polyp at 8 cm but contrast examination of the large bowel was normal. Repeated cystoscopic biopsy 6 weeks later again showed mucin-secreting colonic mucosa but also showed acute ulcerative cystitis. Laparotomy revealed a capacious bladder, no evidence of colovesical fistula and induration to the right wall of the bladder. On cystotomy this was found to be due to a well circumscribed lesion measuring 2.5 cm in diameter. This was excised with macroscopic clearance. Histological examination showed full thickness bladder wall in which there was extensive ulceration with fibrosis and active inflammation. The epithelium was of the complex glandular mucin-secreting intestinal type. This showed severe dysplasia with multi-layering, nuclear atypia, hyperchromasia and pleomorphism. The microscopic changes extended to the resection margin. Follow-up cystoscopy was undertaken 3 months later and although this showed no macroscopic lesion, biopsies from the scar and "normal" mucosa both showed evidence of intestinal metaplasia but now without dysplasia.

Comment

Cystitis glandularis is a recognised metaplastic response to urinary tract irritation but also occurs in as many as 60% of asymptomatic bladders examined at autopsy (Weiner *et al.*, 1979). The hallmark of CG is mucin-producing glandular epithelium similar and sometimes identical to intestinal mucosa both histologically and histochemically. The ultrastructure features are comparable to those of normal colonic mucosa. Complex glandular metaplasia simulating intestinal mucosa is rarely seen in the non-exstrophic bladder and is associated with a significant risk of malignancy (Bullock *et al.*, 1987). Intestinal metaplasia has been reported to progress to adenocarcinoma at intervals of 5 to 15 years (Susmano *et al.*, 1971). Adenocarcinoma accounts for 0.5 to 2% of all bladder tumours (Anderstrom *et al.*, 1983). In the westernised population non-metastatic adenocarcinoma is seen most often in association with urachal remnants and exstrophy. A further category of primary adenocarcinoma is that arising from complex glandular metaplasia. In common with colonic neoplasms, and in contrast to those of urachal origin, these primary adenocarcinomas of the bladder produce sulfomucins.

Regardless of the aetiology, survival rates for primary adenocarcinoma of the bladder are poor, with only 18% of patients surviving 5 years (Anderstrom *et al.*, 1983). The factors resulting in

the transition from intestinal metaplasia to adenocarcinoma are not clear but include the persistence of irritative factors such as urinary infection, bladder calculi and bladder outlet obstruction. These should be managed aggressively and follow-up histology obtained. Our patient is reluctant to have definitive surgery for outlet obstruction and disinclined to stop cigarette smoking. The urine is currently sterile and he is being kept under review.

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Cystitis Emphysematosa

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Cystitis emphysematosa, the presence of gas-filled vesicles in the wall of the bladder, was described originally as a pathological entity only. It is a rare condition (Cohen *et al.*, 1984) found in patients who are diabetics, those who have bladder outflow obstruction or both. A review of the literature was carried out by Bailey (1961) and of the 19 cases he reported, 15 had diabetes and 12 grew *Escherichia coli* in the urine.

Case Report

A 65-year-old man was admitted from a long-stay psychiatric hospital complaining of nausea, vomiting and abdominal distension. He had had a retropubic prostatectomy for benign prostatic hyperplasia 12 years



Fig.

previously and had recurrent symptoms of outflow obstruction. Investigations revealed haemoglobin 6.7 g/dl, WBC count 15,000/mm³, blood urea 14.7 and blood sugar 7 mmol/l. An abdominal X-ray showed a massively enlarged bladder with intravesical and intramural gas (Fig.). Urethral catheterisation was unsuccessful. Ultrasound confirmed bilateral hydronephrosis and a suprapubic drain was inserted, producing a prolonged diuresis. A urine sample showed white cells and bacteria and culture revealed a heavy growth of *Escherichia coli* only. Contrast studies failed to show any enterovesical fistulae. Cystoscopy revealed a posterior urethral stricture requiring a urethrotomy. Treatment was completed with a course of trimethoprim for 7 days.

Comment

This florid case of cystitis emphysematosa is presented in a man who was not diabetic but who had chronic outflow obstruction only from a urethral stricture.

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Points of Technique

Bladder Carcinoma—Free Flap Surgery for the Unhealed Perineal Sinus

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The unhealed perineal sinus poses considerable management difficulties. We report the use of a free flap technique to achieve healing in a patient with late sequelae of ablative surgery and radical radiotherapy for carcinoma of the bladder.

Case Report

A 52-year-old man with a 2-year history of invasive transitional cell carcinoma of the bladder presented with a persistent perineal sinus associated with foul discharge and intractable pain. The tumour had initially been managed by transurethral resection, followed by radical radiotherapy and, later, total cystectomy with ileal conduit formation. An anterior resection and subsequent excision of the rectal stump were performed in attempts to resolve severe radiation proctitis. Examination revealed a miserable, cachectic man with an unhealed fist-sized perineal defect, which was debrided prior to definitive surgery.

The cavity was filled with the bulk of a latissimus dorsi myocutaneous free flap, using a skin paddle over the fully harvested muscle to allow tension-free primary closure. Microvascular anastomoses of the 10.5 cm subscapular vessel pedicle were performed to the femoral artery and long saphenous vein well outside the irradiated area (Fig. 1). The donor site defect was closed directly. Subsequent healing was uneventful and 3.5 years later the perineum remained intact and painless.

Comment

Successful closure of a chronic perineal sinus by the use of a free flap technique has not previously been described. In order to achieve healing in an area of chronic suppuration, devitalisation and poor capacity for repair, well vascularised tissue with normal potential for healing (Graham, 1965) and immunological activity (Chang and Mathes, 1982) has to be transferred into the perineum.

Treatment by radical excision with coccygectomy, distal sacrectomy and split-skin grafting do not fulfil these criteria. Pedicled thigh muscle flaps are limited by their small bulk, arc of rotation and

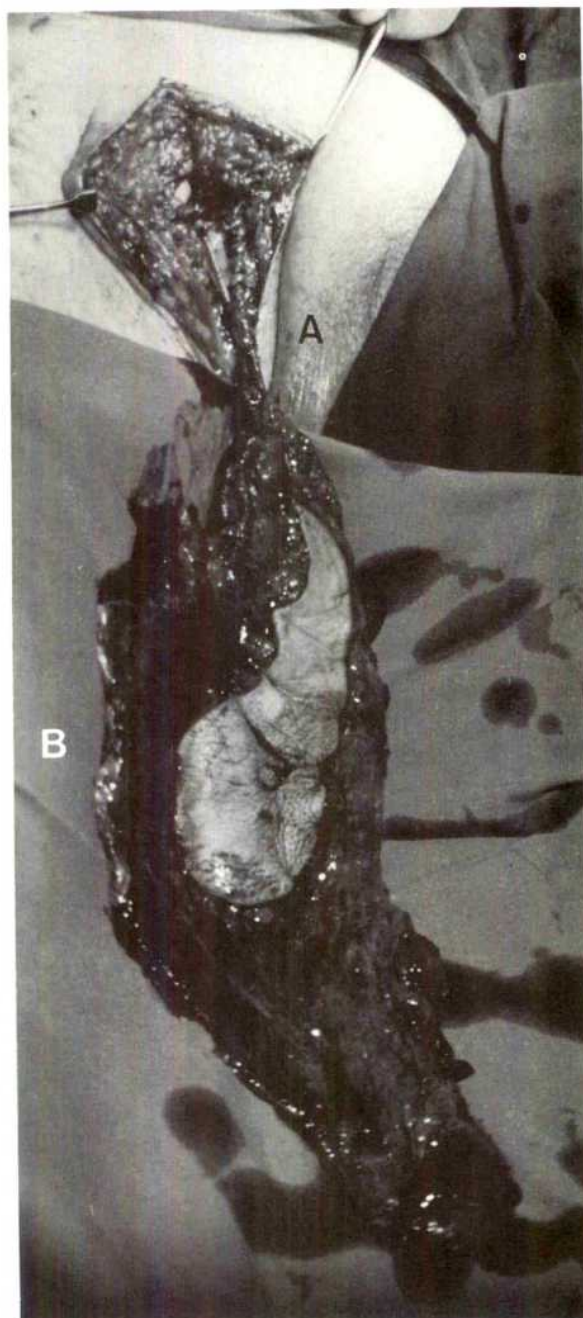


Fig. 1 Abundantly perfused free latissimus dorsi myocutaneous flap demonstrating (A) the 10.5 cm vascular pedicle and (B) the bulk of muscle available to fill the perineal defect.

uncertain distal blood supply. A rectus abdominis pedicle flap involves an extensive abdominoperineal approach (Young *et al.*, 1988).

The latissimus dorsi free myocutaneous flap

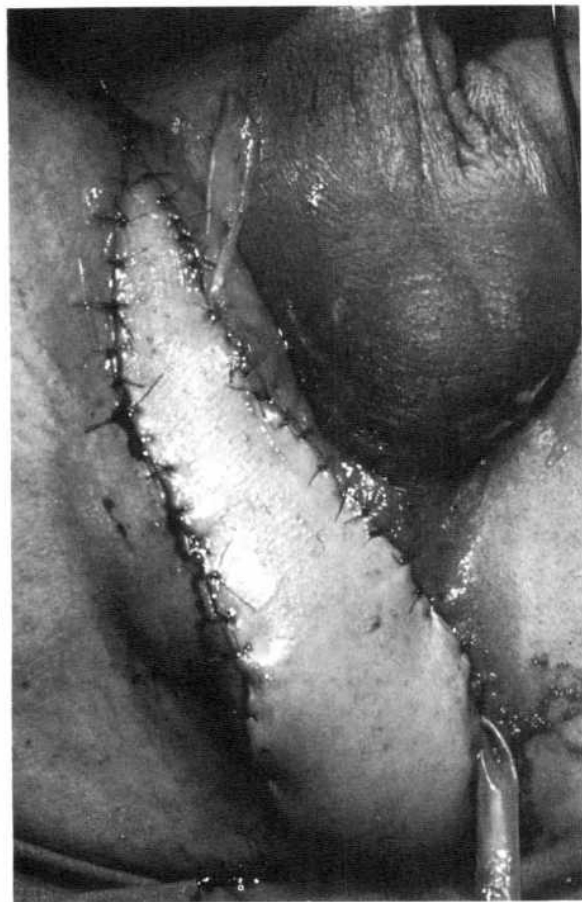


Fig. 2 Immediate post-operative result of tension-free insertion of free flap into a chronic post-irradiation perineal sinus.

provides a large bulk of immunologically active tissue with a certain blood supply and a skin paddle permitting tension-free closure of the perineum (Fig. 2). The long vascular pedicle allows safe anastomosis within normal tissue. The technique is proposed as a valuable addition to the methods of treatment of the persistent perineal sinus.

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Selective Flushing (Seldinger Technique) in the Management of Gravel Retained in a Calix following Extracorporeal Shock Wave Lithotripsy

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Even small, non-obstructive caliceal stones can be responsible for pain and recurrent urinary tract infection. Percutaneous nephrolithotomy and extracorporeal shock wave lithotripsy (ESWL) have replaced open nephrolithotomy as the treatments of choice in these cases—sometimes in combination (Brannen *et al.*, 1986; Mee and Thuroff, 1988; Netto *et al.*, 1989). Gravel following ESWL can be retained or accumulate in apparently normal or even wide-necked calices, especially the lower ones. Further aggregation is then a risk. We present an alternative auxiliary method for removing the retained fragments.



Fig. 1 Pre-treatment intravenous urogram.



Fig. 2 Pre-treatment tomography.



Fig. 4 Tomography 1 month after the second ESWL.



Fig. 3 Tomography 2 months after the first ESWL.

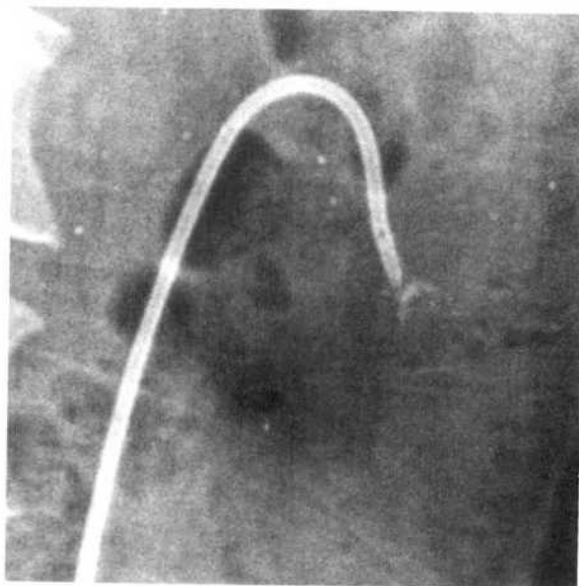


Fig. 5 Angiographic catheter placed in the lower calix.



Fig. 6 Intravenous urogram 3 months after flushing.

Case Report

A 58-year-old woman underwent ESWL (Wolf Piezolith 2300) for a left-sided renal stone (Figs 1 and 2). She still had symptoms 2 months later and follow-up tomography demonstrated disintegration, but also gravel in the lower calix (Fig. 3). Further ESWL (3500 shock waves) was performed but the fragments did not pass (Fig. 4). One month later an angiographic catheter (6.3 F) with a flexible tip was guided to the renal pelvis and the tip placed in the lower calix. A 50-ml syringe with isotonic saline solution was used to flush the calix through the catheter with small volume jets under high pressure. Fluoroscopy was used to monitor the clearance of the fragments and after 8 flushes the calix was emptied (Fig. 5). There were no complications during or following the procedure. The patient had no symptoms at follow-up 3 months later and tomography and intravenous urography were normal (Fig. 6).

We find this method in selected cases to be a safe alternative to a percutaneous procedure.

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Knotting of Suprapubic Epidural Catheter with Urethral Filling Tube. An Unusual Complication of Pressure-flow Study

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Case Report

A 45-year-old female with frequency of micturition and incomplete voiding was referred for urodynamic evaluation.

A 10 F infant feeding tube was passed *per urethram* during a pressure-flow study. After filling the bladder, a suprapubic 5 F epidural catheter was passed with the aid of a 14 F intracath (Viggo). It has been our practice to

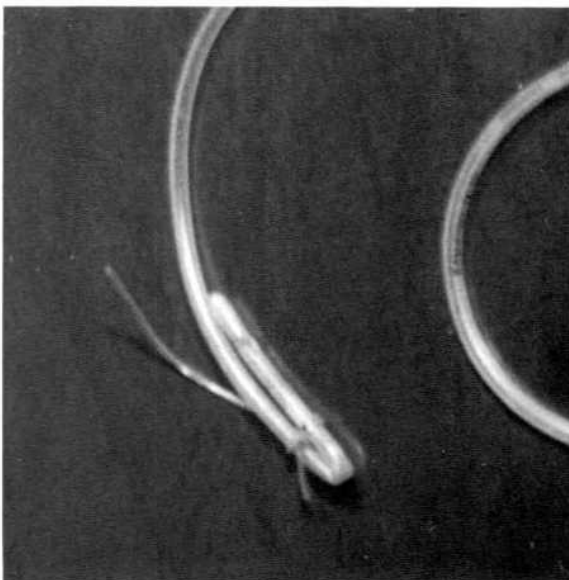


Fig. Knotted epidural catheter around infolded filling tube.

push a good length of the epidural catheter into the bladder to avoid displacement of the catheter during changes of posture and provocation tests. The study was started using the urethral tube for filling and the epidural catheter for monitoring intravesical pressure (Abrams, 1984). The vesical pressure line showed no changes during either filling or provocation and flushing revealed a blocked epidural catheter. Attempts to pull out the epidural catheter met with resistance and it broke. We then pulled out the urethral filling tube, also with difficulty. It was then found that the epidural catheter was knotted around the infolded infant feeding tube (Fig.).

Comment

There is an advantage in using a suprapubic tube to measure pressure. Pressure measurement with a per-urethral tube disturbs voiding and obstructs the urethra. We have not encountered this complication in more than 100 such studies. Edwards and Powell (1986) described a complication of the urethral pressure profile where bladder mucosa was trapped

in a knot, and McInerney and Stephenson (1989) described knotting of an angiographic catheter with an 8 F filling catheter passed *per urethram*.

One should not push the suprapubic pressure line too far into the bladder and it should be fixed with adhesive to avoid inadvertent displacement and possible knotting.

References

- Abrams, P. H. (1984). The practice of urodynamics. In *Urodynamics. Principles, Practice and Application*, ed. Mundy, A. R., Stephenson, T. P. and Wein, A. J. First edition. Chapter 8, pp. 76–92. Edinburgh: Churchill Livingstone.
- Edwards, L. E. and Powell, C. S. (1986). Urodynamic studies: an unusual complication. *Br. J. Urol.*, **58**, 461–462.
- McInerney, P. D. and Stephenson, T. P. (1989). Knotting of pressure lines during urodynamics. *Neurourol. Urodynam.*, **8**, 243–244.

Requests for reprints to: A. Kumar, Department of Surgery, Prince Henry's Hospital, St Kilda Road, Melbourne, Victoria 3004, Australia.

Correspondence

Dear Sir,

re Renogastric fistula. T. de Cervens *et al.* *Br. J. Urol.*, **68**, 321–322, 1991.

The authors describe an interesting case of renogastric fistula in a middle-aged woman with a “long history of left loin pain”. Our recent experience with such a fistula (Stephenson and Evans. *Br. J. Hosp. Med.*, **45**, 387, 1991) prompts this correspondence.

Our female patient was only 24 years of age and in addition to possibly being the youngest case in the literature, other than those developing such fistulae following abdominal trauma (Bissada *et al.* *J. Urol.*, **110**, 273–276, 1973), she initially presented with diffuse purulent peritonitis as a result of free intra-peritoneal rupture of an infected left upper pole renal cyst. Furthermore, our patient’s history was only of a matter of weeks. Although she made

a rapid recovery following laparotomy and peritoneal lavage, a troublesome renogastric fistula subsequently developed.

The management of infected renal cysts no longer necessitates an open operation as a successful outcome can be achieved by a combination of percutaneous aspiration and parenteral antibiotics (Stables and Jackson. *Br. J. Radiol.*, **47**, 290–292, 1974). To avoid the morbidity associated with infected renal cysts and the possible development of either renovisceral or renocutaneous fistulae (Abeshouse. *Urol. Cutan. Rev.*, **53**, 641–671, 1949), we would recommend close follow-up of patients suspected of harbouring such lesions. Early diagnosis of cyst recurrence is essential and may be an indication for prompt surgical intervention.

Yours faithfully,

B. M. Stephenson and A. G. Evans
Department of Surgery, Princess of Wales Hospital,
Bridgend.

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21-26 June 1992

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Scholarships for Experimental and Clinical Research in Urology

The European Association of Urology and the European Board of Urology will award three scholarships for research in Urology. Each scholarship will be awarded for one year, starting on 1 July 1992, at a maximum of 33,000 ECU at any appropriate institution in the world. Further information from: The European Board of Urology Education Committee, P.O. Box 25285, 3001 HG Rotterdam, The Netherlands. Tel: 31.10.436.6665. FAX: 31.10.436.6669.

British Journal of Urology Travelling Fellowship

This fellowship of £1500 enables a Senior Registrar or numbered Career/Research Registrar to attend the Annual Meeting of the American Urological Association. It is awarded in April each year at the Annual Scientific Meeting of the Senior Urological Registrars Group (SURG). The award is given for the best paper presented at this meeting on a vote by the members of SURG present at the meeting. Invitations to the meeting are sent out in January by the Chairman of the Senior Urological Registrars Group and papers must be new work not previously published and not resulting from a thesis. An additional Fellowship may be awarded at the discretion of the British Journal of Urology and the Senior Urological Registrars Group.

Lewis Medical Travelling Scholarship

The scholarship covers travel, accommodation and registration expenses associated with attending the Annual Meeting of the American Urological Association. The scholarship will be available to any person appointed to a numbered urological training post and will be awarded to the person presenting the winning paper at the Annual Meeting of the Senior Urological Registrars Group. An additional scholarship may be awarded at the discretion of the Senior Urological Registrars Group and Lewis Medical Limited.

Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. The prize will be awarded at the Annual Meeting of the Association.

Canadian Urological Association Meeting

Winnipeg, Canada. 21-25 June 1992

Further particulars from: Dr Denis H. Hosking, GE-446, 700 William Avenue, Winnipeg, Manitoba R3E 0Z3, Canada.

Edinburgh Urological Festival

Edinburgh. 24-27 August 1992

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.

Shackman Travelling Fellowship 1993

Applications are invited from Medical Practitioners registered in the United Kingdom who are either trainees in Urology or Organ Transplantation or Consultant Urological Surgeons or Consultant Surgeons with a major commitment to transplantation of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide suffi-

cient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for application is 1 September 1992.

Further particulars and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB2 9AG.

Obituary

Mr David M Wallace, CBE

Mr David Wallace died on 11th January 1992 at the age of 78. Surgeon to St Peter's Hospital and the Royal Marsden Hospital, he will long be remembered for his outstanding contributions to urological oncology and especially to bladder cancer. His book "Tumours of the Bladder" (1959) summarised much of his work; his determined support of early epidemiological studies led to important observations that influenced industrial compensation for patients with bladder cancer. He will also be remembered for his operative techniques for uretero-ileal anastomosis and for his contribution to the first controlled clinical trial for advanced bladder cancer. Amongst his many distinctions, Mr Wallace was a President of the Section of Urology of the Royal Society of Medicine in 1971-1972 and he was awarded the St Peter's Medal in 1973.

Diary

1992

- March 19–21** Eleventh International Symposium of Operative Andrology. Istanbul, Turkey. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
- March 19–21** Searching for Prostatic Carcinoma: the Problem of Screening and Early Detection. Munich, Germany. Contact: D. Née, Secretariat, Department of Urology Krankenhaus der Barmherzigen Brüder, Romanstr. 93, W-8000 Munich 19, Germany. Tel: 89/1793-252 or 89/17 56 61. FAX: 89/1782653.
- March 26–27** Eighth Annual Symposium on Progress in Paediatric Surgery, Oviedo, Spain. Contact: Dr J. L. Teixidor de Otto, Servicio de Cirugía Pediátrica, Hospital Central de Asturias, Centro Universitario, E-33006 Oviedo, Spain.
- April 3–5** Third International Conference on Geriatric Nephrology and Urology. Toronto, Canada. Contact: Dr D. G. Oreopoulos, Peritoneal Dialysis Unit, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8. Tel: 416 364 9974. FAX: 416 360 8127.
- April 9–11** 6th International Urological Symposium. Girne, North Cyprus. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
- April 24–25** Annual Meeting of the Irish Society of Urology. University of Limerick. Contact: Honorary Secretary, Irish Society of Urology, at the Royal College of Surgeons in Ireland, 123 Saint Stephen's Green, Dublin 2, Ireland.
- April 25** HIV: 1992. University of California Davis Medical Center, Sacramento, USA. Contact: Office of Continuing Medical Education, UC Davis Medical Center, 2701 Stockton Boulevard, Sacramento, CA 95817, USA. Tel: (916) 734-5390. Fax: (916) 736-0188.
- May 6–8** 8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.
- May 8** Scottish Task Force on Incontinence—Annual Meeting. Southern General Hospital, Glasgow. Contact: Sister Mary Ballentyne, Continence Resource Centre, Southern General Hospital, Glasgow G51 4TF. Tel: 041 425 1117.
- May 10–14** American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
- May 23–24** Société Belge d'Urologie: 57th Congress. Liège, Belgium. Contact: Dr F. F. Wart, 4 Avenue du Bois des Sartis, B-6111 Landelies, Belgium.
- May 24–28** Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.
- June 4–5** Second International Workshop and Symposium on New Urological Technology. Leuven, Belgium. Contact: Prof. Dr L. Baert, Department of Urology, Brusselsestraat 69, 3000 Leuven, Belgium. Tel: 016-21 75 32.

- June 4-6 Fourth International Meeting of Andrology, Como, Italy. "Treating Male Infertility: New Possibilities". Contact: Dr G. M. Colpi, II Divisione di Chirurgia, Centro di Andrologia e Infertilita, Ospedale "VALDUCE", Via Dante 11, I-22100 Como, Italy.
- June 10-12 Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.
- June 22-25 Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
- June 23-26 BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
- July 22-25 European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
- August 7-9 Ninth Meeting of International Society for Dynamics of the Upper Urinary Tract. Akita, Japan. Contact: Dr Seigi Tsuchida, Department of Urology, Akita University School of Medicine, 1-1-1 Hondo, Akita, 010 Japan. FAX 81-188-36-2619.
- August 24-27 Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
- August 24-27 VIIth International Symposium on Urolithiasis and Related Clinical Research. Cairns, Australia. Contact: Dr Rosemary L. Ryall, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia 5042.
- September 3-6 Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
- September 14-18 Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
- October 9-10 BAUS Autumn Meeting, Swansea. Contact BAUS Office.
- December 4-5 Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.
- 1993
- May 16-20 American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
- June 20-24 Canadian Urological Association Annual Meeting, Bonaventure Hotel, Montreal, Quebec. Contact: To be announced.
- 1994
- May 15-19 American Urological Association, Moscone Centre, San Francisco, California.

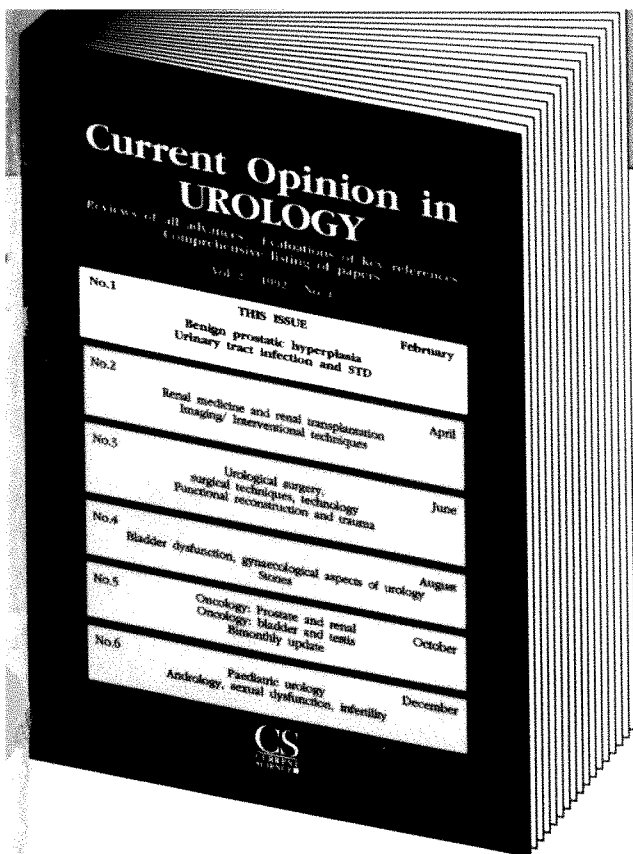
Erratum

re A Consumer's Guide to Commercially Available Urodynamic Equipment. D. G. Barnes, D. Ralph, P. D. Hill, C. A. Lewis, P. J. R. Shaw and P. H. L. Worth.

Br J Urol (1991), **68**, 138–143

The Editor and publishers wish to apologise for having omitted the name of the third author, P. D. Hill, from the list of authors of the above article. We are sorry for the inconvenience that this has caused.

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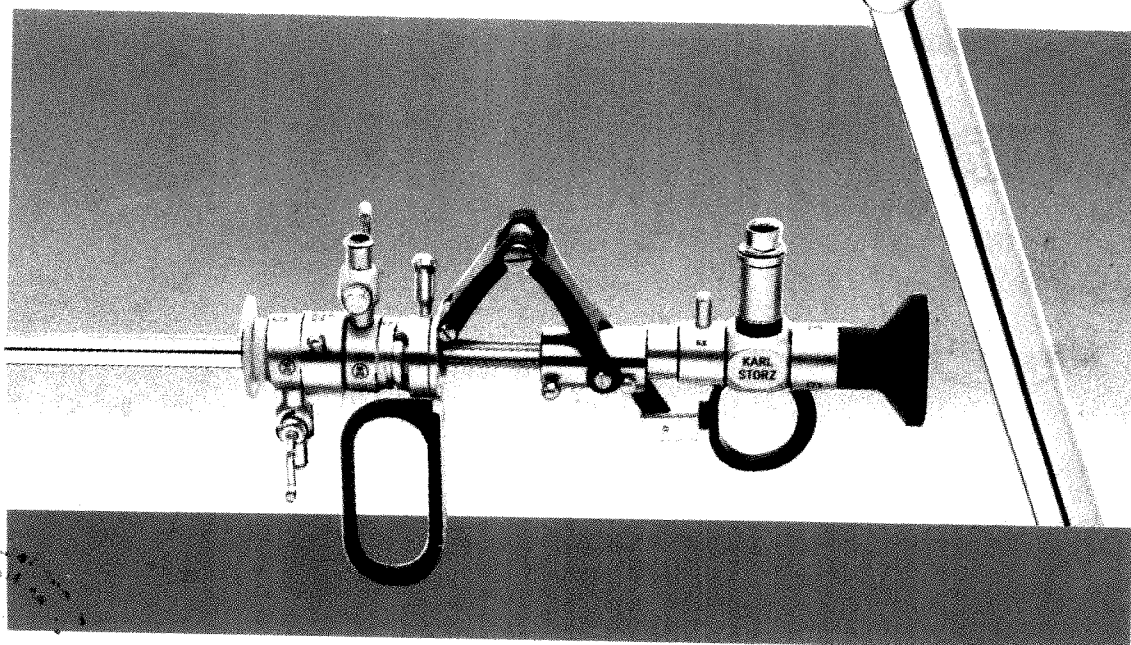
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